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The principal authors of the paper are Suzannah Chapman, Guillaume Dedet, and Ruth Lopert. Eileen Rocard and Thomas Renaud provided research assistance and support to the data analysis; Valérie Paris contributed to the early stages of research and drafting; and Justine Deziel provided administrative support.

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Abstract and key points

- **Medicine shortages have become increasingly common** in a number of countries in recent years and the COVID-19 pandemic has exacerbated the situation. The aim of this paper was to develop further insights into the extent and nature of medicine shortages in OECD countries (pre COVID-19). However, absent both a common nomenclature and harmonised notification systems for reporting shortages, intercountry comparisons, and an overarching global perspective remain challenging. Notwithstanding these challenges, **the number of shortage notifications increased by 60%** over the period 2017 to 2019 in a sample of 14 OECD countries.
- **In OECD's analysis, more than half of all notifications were concentrated in three main therapeutic areas**: medicines targeting the nervous system, cardiovascular system and anti-infectives. In nearly two-thirds of cases, a shortage of a given active substance was reported in more than one country. Shortages affected **predominantly older, off-patent** molecules. However, the **impact on patient health is largely unknown**, given that a notification does not necessarily impact patients adversely if appropriate alternatives remain available and accessible.
- The **multifactorial nature of this issue and complexity of this industrial sector confound root cause analysis**, with **different stakeholder perceptions, poor data quality, and general misconceptions** further complicating understanding of the issue. **Pharmaceutical supply chains are highly complex**, involving multiple stakeholders, often with different procedural steps occurring in multiple countries and/or locations. Nevertheless, in general, shortages may be considered as arising from exogenous factors that increase demand (such as in the case of COVID-19), or exogenous or endogenous factors that limit or reduce supply.
- Several analyses have noted that **shortages**, **as reported by marketing authorisation holders**, are **predominantly due to (exogenous) manufacturing and quality issues** (in about 60% of cases). Manufacturing and quality problems include, for example, production quality issues or defects in any component of a product; shortages of inputs; inventory and storage practices; temporary and permanent suspension of production due to e.g. technical issues with production or non-compliance with Good Manufacturing Practice, or manufacturing site closure or relocation. Linked to this, policy debates also point to the issues of concentration of manufacturing, or limited availability of manufacturing facilities to produce certain categories or components of medicines, as additional sources of supply vulnerability. While the contributions of these factors are challenging to assess based on available information, in general, ensuring that the manufacturing of particular components is not highly concentrated at one or few manufacturing sites or in small geographic areas, could reduce the overall vulnerability of medicines' supply to these types of risks.
- Beyond manufacturing and quality issues, (endogenous) **commercial factors, and the policy settings that influence them**, may play important underlying roles in propagating shortages, particularly for off-patent products, although further analysis is needed. **Regulation and reimbursement policies**, such as those that favour **unsustainably low prices**, may influence commercial decisions, putting supply at risk**.** In the United States, for example, an empirical analysis identified three root causes, key among them a lack of incentive for the continued production of less profitable drugs in a setting of highly competitive tendering and contracting

practices. The analysis also cited a lack of incentives to upgrade production facilities or maintain quality management systems as another root cause. There have also been suggestions that similar issues are implicated in Europe, but the links between production problems and market attractiveness warrant further exploration.

- Many OECD countries are pursuing **policies aimed at improving the monitoring, mitigating the impact, and/or preventing the future occurrence of shortages**. For example, most OECD countries have national monitoring systems, although reporting requirements differ widely across countries and regions. Several countries have implemented a range of measures in an effort to mitigate the impact of shortages, such as simplified regulatory procedures, and obligatory maintenance of supply reserves. Evidence from the United States, which may or may not be generalisable, suggests that preventative measures should target economic and commercial drivers, particularly in off-patent markets.
- However, there is little information on the assessment of the impact of different national policies, and **further research is needed to identify best practices**. In the first instance, **greater harmonisation of national monitoring systems would allow more robust within- and cross-country comparisons**, and a better understanding of the impact on patients, the underlying root causes, and the effects of policy measures. It is also important for countries to implement **multifaceted strategies addressing monitoring, mitigation, and prevention**, to **involve stakeholders** in developing and implementing these, and also to recognise the importance of **downstream communications to health professionals and patients.**
- Overall, while it is evident that **more robust data and further analysis of medicine shortages, their causes, and effective policies are needed**, it is also clear that the **way forward should involve a global approach that engages all relevant actors, national governments and international stakeholders, and addresses issues that go beyond the healthcare sector.**

Résumé et points saillants

- Au cours des dernières années, **les pénuries de médicaments sont devenues de plus en plus courantes dans un certain nombre de pays**, et la pandémie de COVID-19 a exacerbé cette situation. L'objectif du présent rapport est d'approfondir les perspectives sur la nature, l'étendue et les causes des pénuries médicamenteuses dans les pays de l'OCDE (pré-pandémie). Pour autant, l'absence d'une nomenclature commune ainsi que d'une harmonisation des systèmes de notifications des pénuries rendent difficiles l'analyse comparative entre pays ainsi que l'appréciation générale de cet enjeu. En dépit de ces difficultés, dans un échantillon de 14 pays de l'OCDE analysés pour l'occasion, **les notifications de pénuries médicamenteuses ont augmenté de 60 % entre 2017 et 2019.**
- La présente étude rapporte par ailleurs que **plus de la moitié des notifications étaient concentrées sur trois catégories pharmaco-thérapeutiques** : les médicaments du système nerveux, ceux du système cardiovasculaire et les agents anti-infectieux. Dans environ deux-tiers des cas une pénurie de principe actif impactait plus d'un pays à la fois. **Les pénuries concernaient principalement des molécules anciennes et ayant perdu leur brevet**. Cependant**, l'impact réel de ces pénuries sur la santé des patients reste largement inconnu**, une notification n'impliquant pas nécessairement une pénurie affectant les patients si des alternatives appropriées restent disponibles.
- **La nature multifactorielle de ce sujet, la complexité de ce secteur industriel, les perspectives des différents acteurs impliqués et de manière plus générale la paucité d'informations disponibles rendent difficiles une analyse factuelle des causes profondes des pénuries de médicaments**. **Les chaînes d'approvisionnement pharmaceutiques sont très complexes**, impliquant de nombreux acteurs intervenant à différentes étapes de la production, souvent en différents lieux ou pays. De manière générale, les pénuries peuvent tout de même être considérées comme la résultante de facteurs exogènes aboutissant à une augmentation de la demande (comme dans le cas du COVID-19), ou de facteurs exogènes ou endogènes réduisant ou limitant l'offre.
- **Plusieurs analyses ont suggéré que les pénuries, telles que signalées par les titulaires d'autorisations de mise sur le marché, sont principalement dues à des problèmes (exogènes) de fabrication et de qualité (dans environ 60 % des cas).** Ces derniers recouvrent, entre autres, les problèmes de qualité lors de la production ou les défauts de tout composant d'un produit ; les pénuries de matières premières ; les pratiques d'inventaire et de stockage ; les suspensions temporaires ou permanentes de la production dues par exemple à des problèmes techniques sur les chaînes de production ou à une éventuelle non-conformité aux Bonnes Pratiques de Fabrication ; la fermeture ou la délocalisation des sites de fabrication. En lien avec cela, les débats politiques soulignent également le problème lié à la concentration ou à la faible disponibilité des moyens de production pour produire certaines catégories ou composants de médicaments, comme élément ajoutant à la vulnérabilité des chaînes d'approvisionnement. Bien que les contributions respectives de ces différents facteurs soient difficiles à évaluer sur la base des informations disponibles, de manière plus générale, s'assurer que la fabrication de chacun des

composants intervenant dans la production n'est pas fortement concentrée sur un ou quelques sites de fabrication ou dans de petites zones géographiques réduirait la vulnérabilité de l'approvisionnement.

- Au-delà des problèmes de production, **les facteurs commerciaux (endogènes) et les politiques qui les influencent peuvent jouer un rôle sous-jacent important dans la perpétuation de pénuries**, plus particulièrement pour les produits tombés dans le domaine public, même si des analyses plus poussées méritent d'être menées sur ce sujet. **Les politiques réglementaires et de remboursement, notamment celles poussant vers des prix trop bas, peuvent influencer les décisions commerciales**, créant un risque pour l'approvisionnement. Aux États-Unis, par exemple, une analyse empirique a identifié trois causes profondes aux pénuries médicamenteuses. Le manque d'incitations à la poursuite de la production de médicaments moins rentables dans un contexte d'appels d'offres et de pratiques contractuelles hautement concurrentiels était vue comme ayant une importance majeure. L'étude a également cité le manque d'incitations à moderniser les installations de production ou à maintenir des systèmes de gestion de la qualité comme une autre cause profonde des pénuries. Il a également été suggéré que des enjeux similaires se retrouvent en Europe, mais les liens entre problèmes de production et attractivité du marché méritent des explorations plus approfondies.
- **De nombreux pays de l'OCDE ont pris des mesures visant à améliorer le suivi des pénuries, à en atténuer l'impact et à prévenir leur occurrence future**. Par exemple, la plupart des pays de l'OCDE disposent de systèmes nationaux de suivi des pénuries, même si les exigences en matière de notification varient considérablement d'un endroit à l'autre. Plusieurs gouvernements ont mis en œuvre une série de mesures pour tenter d'atténuer l'impact des pénuries, telles que des procédures réglementaires simplifiées et le maintien obligatoire de réserves d'approvisionnement. Les données provenant des États-Unis, qui ne sont pas nécessairement généralisables, suggèrent que les mesures préventives devraient cibler les incitatifs économiques et commerciaux, en particulier pour les produits dans le domaine public.
- Cependant, il existe peu d'évaluation de l'impact en vie réelle de ces mesures et **des recherches supplémentaires seraient nécessaires afin d'identifier de possibles bonnes pratiques**. En tout état de cause, **une plus grande harmonisation des systèmes de surveillance nationaux permettrait déjà des comparaisons plus fiables au sein et entre les pays**, ainsi qu'une meilleure compréhension de l'impact sur les patients et des causes profondes sous-jacentes. Il est également important que **les pays mettent en œuvre des stratégies complètes traitant de la surveillance, de l'atténuation et de la prévention**, **impliquent tous les acteurs** dans leur élaboration et leur mise en œuvre, et également reconnaissent l'importa**nce de la communication auprès des professionnels de santé et des patients.**
- En somme, s'il est certain que **des données plus solides et une analyse plus approfondie des pénuries de médicaments, de leurs causes et des politiques efficaces soient nécessaires**, il apparaît également que la voie à suivre devrait impliquer **une approche globale engageant tous les agents impliqués dans l'approvisionnement et la production, les gouvernements et les acteurs internationaux, en abordant des aspects allant bien au-delà du seul secteur de la santé.**

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1. Introduction

1. Even in the wealthiest economies, access to medicines may be impaired by the increasing frequency of supply interruptions and medicine shortages[1]. This issue has received growing attention in recent years, however, with the onset of the COVID-19 pandemic since this work was commenced, scrutiny of the issue has increased. The *Pharmaceutical Strategy for Europe* adopted in November 2020, for example, includes addressing medicines shortages under the pillar of crisis preparedness and response[2].

2. Substantial information has already been published and a number of actions implemented to address shortages in OECD countries and worldwide, yet issues persist. Prior to the pandemic, shortages were mainly observed and assessed from a national, or in the case of Europe, regional perspective. However, absent both a common nomenclature and harmonised notification system for reporting shortages, intercountry comparisons, and an overarching global perspective, remain challenging. This paper adopts an OECD perspective in an attempt to develop a more comprehensive picture of the issue of medicine shortages, and to identify strategies to address it. The paper is structured as follows:

- Following this Introduction, Section 2. provides some background and context to the issue of medicine shortages, presenting an overview of the various concepts, reporting mechanisms, monitoring systems, and (pre-pandemic) trends in OECD countries.
- Section 3. presents some insights into the magnitude and scope of the medicine shortages issue in OECD countries, based on a cross-country analysis of data from 14 countries (Austria, Belgium, Canada, Estonia, France, Germany, Hungary, Iceland, Latvia, Norway, Portugal, Sweden, Switzerland, and the United States) covering the period 2017-2019.
- Section 4. explores some of the possible causes of, and supply chain vulnerabilities contributing to medicine shortages, drawing on published literature, insights from national monitoring systems, and international trade data.
- Section 5. reports on policy measures taken by OECD countries to address the issue of medicine shortages, and which could inform efforts to develop a more comprehensive and coordinated response to this global challenge.
- Supplementary materials 1 and 2 provide supporting information: 1) OECD analysis of national shortage monitoring systems; and 2) International trade flows of selected groups of medicines.

3. The analysis presented in this paper drew extensively on published and grey literature, data from official websites, and opportunistic consultations with various stakeholders in 2019 and 2020. This paper focuses predominantly on the situation *prior* to the COVID-19 pandemic. The pandemic has since brought with it a number of unique and novel challenges, which will require further analysis in order to enhance preparedness for future crises.

[1] As formal definitions vary significantly from country to country, the term "medicine shortage" in this paper refers to any supply disruption or sudden change in the supply-demand equilibrium of a marketed pharmaceutical product that leads to an actual or anticipated lack of stock on the shelf for patients. An anticipated shortage may be preventable. Shortages include both temporary and permanent supply discontinuations (i.e. withdrawal from the market); the latter are sometimes referred to as "availability issues".

[2] See https://ec.europa.eu/health/human-use/strategy_en, accessed December 2020.

2. Defining medicine shortages

4. Before estimating the magnitude and scope of the medicine shortage situation in OECD countries, it is important to understand the various concepts, reporting mechanisms, and monitoring systems that make international comparisons complex. Not all countries monitor this issue, and those that do use monitoring systems that differ substantially from one another. The overall objective of this section is thus to provide some context to the discussion by presenting a brief overview of the pharmaceutical supply chain (Section 2.1), outlining the various shortage definitions (Section 2.2), providing an overview of monitoring systems in OECD countries (Section 2.3), and discussing the trends reported in the literature (Section 2.4). The presented overviews of shortage monitoring systems in OECD countries are current as of March / April 2020, with updates for some countries drawing on information collected by Vogler and Fischer (2020[1]) in August 2020. Additional information can be found in Supplementary Material 1, which also includes a list of national reporting registers in Table 1.

2.1. Some insight into the nature of pharmaceutical supply chains is important to understanding medicine shortages

5. **Pharmaceutical supply chains are often very complex, involving multiple steps, with the potential for each step to be undertaken in a different facility, and even in a different country[3]**. Figure 2.1 provides a simplified schematic of the pharmaceutical supply chain, illustrating the steps from manufacturing, to distribution and storage, and to delivery to the final stakeholder in the distribution chain (e.g. the community pharmacy, the hospital, etc.) and thence to patients. Stakeholders involved in the process include suppliers of raw materials, manufacturers (both of active pharmaceutical ingredients (APIs) and finished products), marketing authorisation holders (MAH), wholesalers / distributors, prescribers, dispensers (e.g. pharmacists), and patients.

6. A simplified account of the steps involved in the production of a small-molecule (non-biological)[4] medicine is described below.

- *Raw materials:* chemical compound used as a base material for the extraction of intermediates.
- *Intermediates:* chemical compound used as a building block, participating in further reactions.
- *Active Pharmaceutical Ingredient (API), or active substance:* chemically active component of a drug product, meant to produce the intended effect in the body.
- *Finished pharmaceutical product (FPP)* [5]: dosage form of the API, mixed with inactive excipients to stabilise the medicinal product and enhance it, often in sterile and secure packaging.

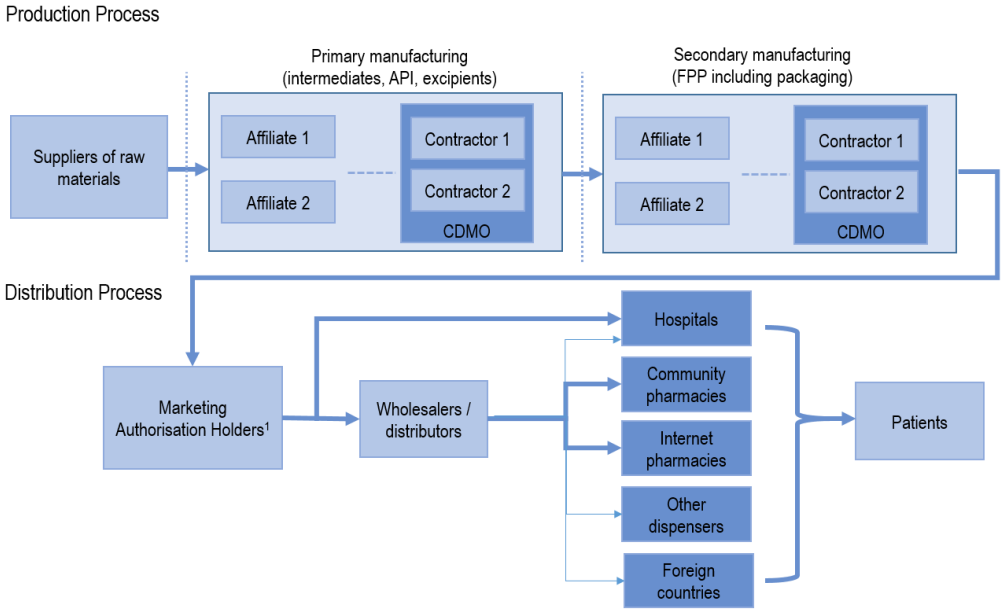
[3] Detailed overviews of prescription drug supply chains in the United States context, for example, are available at https://aspe.hhs.gov/reports/prescription-drug-supply-chains, accessed October 2021.

[4] Biologicals are a class of medicines manufactured in, or sourced from, living systems such as microorganisms, or plant or animal cells. Processes and supply chains for biological medicines are often more complex.

[5] See WHO QAS Terminology- List of Terms and related guidelines (pg. 57-58), available at https://www.who.int/medicines/services/expertcommittees/pharmprep/20111208_QASterminologyDB.pdf (accessed December 2020). Note that a FPP may contain more than one active ingredient and/or excipient. The term “active

7. Primary manufacturing sites are responsible for the production of APIs from raw materials. Secondary manufacturing is concerned with taking the API produced at the primary site and creating from it the FPP (excipients are added to APIs at this stage). Secondary manufacturing sites are often geographically separate from primary manufacturing sites[6]. Note, however, that some manufacturing facilities produce both APIs and FPPs. There are often many more secondary manufacturing sites than primary ones, serving local or regional markets (Shah, 2004[2]). Marketing authorisation holders may rely on contractors to manufacture their products. These contractors may operate under a contract development manufacturing organisation (CDMO) and this can give rise to complex supply chain coordination issues. Once a medicine is produced and the batch is released, it must be transported from the manufacturing site, stored at the wholesaler, and distributed to the end retail point of dispensing. Here, wholesalers are the principal stakeholder, however hospitals frequently source their products directly from MAHs, bypassing wholesalers (Figure 2.1).

Figure 2.1 Pharmaceutical supply chains are generally very complex



Note: Dotted vertical line represents the possibility of an international border. API active pharmaceutical ingredient; FPP finished pharmaceutical product; CDMO contract development manufacturing organisation. 1. This includes parallel traders, who are only relevant for distribution of products within the EU/EEA market. Parallel traders can act by buying from one wholesaler in one country, to another wholesaler in another country. They can supply third country markets, as well as community pharmacies, internet pharmacies, and other dispensers.
Source: Authors.

2.2. Definitions of a "medicine shortage" vary from country to country

8. The terminology used to describe medicine shortages varies from country to country (see Box 2.1 and Supplementary Material 1). **However, most OECD countries consider a medicine shortage to exist when supply is insufficient to meet demand at national level, and may include both temporary or permanent discontinuations** (i.e. withdrawal from the market). Some countries go further and include a minimum duration of supply disruption in the definition (e.g. Austria, Finland, France, Germany, Latvia,

substance" is used throughout the report to refer to the central ingredient, or combination of ingredients, which are responsible for the intended biologic effect of the product.

[6] This may, in some cases, be the outcome of tax and transfer price optimisation within companies.

and Sweden), or time frame for reporting an anticipated shortage (e.g. within the next six months in Australia).

Box 2.1. Definitions of a medicine shortage

It is widely known that formal definitions, or related terms, used to describe medicine shortages vary from country to country (see for example (De Weerdt et al., 2015[3]; Acosta et al., 2019[4]; Vogler and Fischer, 2020[1]; Troein et al., 2020[5]). In response to the Sixty-ninth World Health Assembly resolution WHA69.25 on addressing the global shortage of medicines and vaccines, the World Health Organization in 2017 proposed a draft definition of shortages, taking into account both the demand- and supply-side (World Health Assembly, 2017[6]). A follow-up global survey in 2018 found challenges in the comparability of definitions used by countries (World Health Organization, 2020[7]) In 2019, in a scoping review of studies on shortages, Acosta et al. presented definitions for shortages, or related terms, for sixteen countries found through the literature and institutional websites. Definitions covered both medicine shortages and interruptions of supply. Countries adopted definitions from different perspectives, including that of a *shortage* and aspects related to *supply chain management*, *market determinants*, or *scarcity*. A few countries also included a duration of supply interruption within their definition (Acosta et al., 2019[4]).

At the European level in December 2016, the European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) created an *HMA/EMA Task Force on the Availability of Authorized Medicines for Human and Veterinary Use* (TF-AAM) to develop and coordinate actions related to shortages of human and veterinary medicines and ensure continuity of supply. The EMA, HMA, and stakeholders (including all Member States) agreed on the following broad definition, which was published on 1 July 2019 in the *Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)* (EMA, 2019, p. 2[8]) (see Supplementary Material 1 for explanations of the individual terms used in this definition):

> *A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level.*

However, in a white paper assessing reporting of medicine shortages in 11 EU countries, authors found that national definitions for 8 of the 11 countries were aligned to just half of this EMA definition when it was broken down into four constituent parts (key term, owner of notification, criteria and scope) (Troein et al., 2020[5]). While alignment is expected to improve given the recent introduction of this definition, this shows the great variability in interpretation and limited cross-country comparability of shortage notification information.

In the EU "single point of contact (SPOC)" network (i.e. network of shortage experts, composed of representatives from national competent authorities of EU-27/EEA countries, EMA and the European Commission), the distinction between "shortages" and "availability issues" is made, and both events are defined differently. On the one hand, "shortages" are considered temporary market disruptions (often linked to manufacturing difficulties/capacity or surge in demand) where stock is meant to be back after a period of time. On the other hand, "availability issues" are defined as temporary or permanent marketing cessations (i.e. withdrawals) where products may be discontinued permanently (i.e. unavailable) often associated with economic/business aspects (company-driven decisions) [1].

Note: See Table 2, Supplementary Material 1 for further details on shortage definitions used by OECD countries.
Source: Authors based on sources cited. 1. See https://www.ema.europa.eu/en/documents/annual-report/2019-annual-report-european-medicines-agency_en.pdf, accessed December 2020.

9. As formal definitions vary significantly from country to country, the term "medicine shortage" in this paper is used to refer to any supply disruption or sudden change in the supply-demand equilibrium of a

marketed pharmaceutical product that leads to an actual or anticipated lack of stock on the shelf for patients. An anticipated shortage may be preventable. Shortages include both temporary and permanent supply discontinuations (i.e. withdrawal from the market); the latter are sometimes referred to as "availability issues".

2.3. Most OECD countries have national reporting systems for medicine shortages, but comparisons are challenging

10. **Most OECD countries have a national (government-based) notification system for reporting actual or expected medicine shortages, but differences exist in the content of these notifications** (Table 1, Supplementary Material 1). In countries with such systems in place, online databases displaying actual or expected shortages of medicines at the individual *product-level*[7] are usually publicly available. However, in addition to definitions of shortages, national notification processes and requirements need to be understood in order to compare notification data between countries. Table 3 in Supplementary Material 1 provides a summary of some of these aspects in OECD countries.

11. **Marketing Authorisation Holders (MAH) are obliged to notify shortages to national competent authorities in all OECD countries** for which information was available at the time of review, with the exception of Japan and New Zealand[8]. In some countries, sanctions may also be possible in the event of non-compliance with reporting requirements. In Denmark, Iceland, Ireland, Latvia, Norway, Slovenia, Switzerland and the United States, voluntary notifications may also be made by wholesalers, pharmacies (community and hospital), patients, doctors and other health care professionals. However, in these cases, the competent authority is likely to confirm the expected shortage with the MAH.

12. **The timing of notification varies across countries**. In EU countries, MAHs are legally obliged to report to national authorities shortages of authorised medicines at least two months prior to the expected shortage. Article 23a, 2nd paragraph of Directive 2001/83/EC and article 27a, 2nd paragraph of Directive 2001/82/EC states that[9]:

> *(…) if the product ceases to be placed on the market of a Member State, either temporarily or permanently, the marketing authorisation holder shall notify the competent authority of that Member State. Such notification shall, other than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the products.*

13. In addition, in the EU, MAHs are requested to notify to the European Medicines Agency (EMA) shortages of all centrally approved products, with a list of all countries affected. The *HMA/EMA Task Force on the Availability of Authorized Medicines for Human and Veterinary Use* (TF-AAM) published a guidance for MAHs on all requirements for shortage notification across the EU, which includes a proposed notification reporting template for use by individual countries (EMA, 2019[8]). The form highlights the minimum suggested information to be provided to a competent authority in the event of an expected shortage. The guidance will be tested and implemented through a dedicated pilot phase (currently on hold due to the COVID-19 pandemic). In 2018, the HMA/EMA TF-AAM also established a "single point of contact (SPOC)" system (see Box 2.1) that aims of to improve the efficiency and responsiveness of the

[7] In this paper, "individual product-level" refers to notifications based on presentation (brand name/strength/form/pack-size).

[8] Note that notification by the MAH was not mandatory in Austria and Germany during the time period for quantitative data analysis (2017-2019) presented in Section 3. of this paper.

[9] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use: https://ec.europa.eu/health/system/files/2016-11/dir_2001_83_cons_2012_en_0.pdf (accessed June 2020).

EU regulatory network regarding availability issues of medicinal products in Europe. The SPOC Network also offers a platform for discussion and collaboration between Member States.

14. In other OECD countries, competent authorities up to six months in advance of an expected shortage (e.g. Canada, United Kingdom, United States).

15. **Most countries require reporting of all anticipated shortages, regardless of expected duration.** However, some countries specify a minimum duration of shortage requiring notification, ranging from three working days in Belgium, to two weeks in Austria, Germany, and Switzerland, and at least three weeks in Sweden. In France, a shortage longer than 72 hours must be notified.

16. Nearly all countries have an official notification form, template or tool available. **Types of medicine shortages notified in national databases differ across OECD countries and data are not necessarily located in a central repository**. Table 4 in Supplementary Material 1 provides an overview of the type of information reported in existing shortage databases in OECD countries, as well as the frequency of updates. It is important to note that the amount of information provided in an individual shortage notification varies by country, and it is not necessarily available in a form that can be extracted and analysed easily.

17. While most countries report on medicine shortages for all marketed products, **some only report or publish data on those affecting a subset of products, such as prescription-only medicines or products deemed to be critical or essential to their respective health systems**. In France, for example, the French National Agency for Medicines and Health Products Safety (ANSM) mandatory reporting applies only to those medicines for which there is major therapeutic interest (*Médicaments d'Intérêt Thérapeutique Majeur* [MITM]), i.e. drugs for which a shortage would be life-threatening or represent a loss of treatment opportunity for patients with a severe disease[10]). In Switzerland, MAH are only required to report shortages to the Federal Office for National Economic Supply (FONES) for "essential drugs" included in a list of active ingredients updated every two years[11]. The US Food and Drug Administration's (FDA) Drug Shortage Program also focuses primarily on products which are life-supporting; life-sustaining; or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery[12]. While reporting of all shortages by MAH is mandatory in Australia, an online database only publishes information on shortages that have critical patient impact. This includes those medicines on a "Medicines Watch List", or those for which a shortage could have a life-threatening or serious impact on patients and for which there is unlikely to be sufficient supply of substitutes[13].

18. **Both current and anticipated shortages are commonly displayed in countries' online registers,** with most also showing resolved shortages for a limited period of time (e.g. those resolved within the preceding six months in Ireland and the United States). Most countries also include medicines that have been withdrawn from the market. In Austria's register, in line with legislation at the time of this review, two types of shortage were reported: "partially available" (i.e. product can no longer be supplied continuously or in sufficient quantities) or "out of stock" (i.e. product can no longer be dispensed).

19. **National notifications of shortages in national databases are often made at individual product-level, but the publicly accessible content of databases varies substantially**. Table 5 in

[10] The complete list of French MITM can be consulted here: https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000032958454&categorieLien=id (accessed November 2021)

[11] See https://www.bwl.admin.ch/bwl/de/home.html (accessed November 2021).

[12] See https://www.accessdata.fda.gov/scripts/drugshortages (accessed November 2021).

[13] The list of critical medicines shortages collated by the Therapeutic Goods Administration in Australia can be found at https://apps.tga.gov.au/prod/MSI/search (accessed November 2021).

Supplementary Material 1 details the different types of variables presented in some shortage notifications databases. While detailed information may be requested, not all information collected is made publicly available in all databases. At the time of review, all countries listed in Table 5 in Supplementary Material 1 included notifications based on brand name/strength/form, with some also reporting pack size. With the exception of the Czech Republic, Israel, Spain, the Slovak Republic and Slovenia that identify products in their databases by brand name, all databases listed either the active substance (International Non-proprietary Name, INN) or Anatomical Therapeutic Chemical (ATC) classification[14]. Anticipated and/or actual start and end dates are shown in most databases, although data may often be missing. The reason for the shortage and the availability of alternative products are also presented in some databases.

20. Finally, **additional online shortages databases are held by non-government entities, and the parameters of the shortage situation may differ from assessments of national authorities.** For example, shortage databases are held by pharmacist and other stakeholder associations in certain countries (e.g. Australia, France, Ireland, the Netherlands, Portugal, Spain, Switzerland, the United Kingdom and the United States)[15]. Bochenek et al. (2018[9]) reported that, in Switzerland, an independent database received ten times the number of notifications of shortages than the Federal Office for National Economic Supply (FONES). Similarly, in a report published by the Society of Hospital Pharmacists of Australia, the number of products found to be in shortage in a point prevalence survey was 365, while only 54 were reported on the official website (SHPA, 2017[10]). By contrast, a Dutch observational study found that authorities (i.e. the Medicines Evaluation Board and Health and Youth Care Inspectorate) detected more than double the number of signals of potential shortages than pharmacy practice (i.e. the Royal Dutch Pharmacists Association), although authorities were notified later (Postma et al., 2018[11]). In this study, there was also little overlap in the types of shortages notified (ibid.).

2.4. Despite a lack of harmonisation, medicine shortages appear to be a growing issue in OECD countries

21. The **magnitude of the shortage situation is challenging to measure, and perceptions of the problem differ between stakeholders[16].** The growing occurrence of medicine shortages is matched by an increasing number of academic publications on this topic in recent years. Between 70 to 115 published articles with the key word ‘‘drug shortages’’ were indexed in PubMed each year since 2011, compared with 24 to 30 annually for the period 2002 to 2010 and fewer than 10 annually prior to 2002 (Videau, Lebel and Bussières, 2019[12]).

22. While differences in reporting definitions and data collection limit international comparisons (see Sections 2.2 and 2.3), **shortages have been examined at an international level.** A 2020 IQVIA analysis, for example, examined MAH-reported medicine shortages in a sample of 11 EU countries[17] using existing publicly available data (Troein et al., 2020[5]). Notwithstanding the data limitations, the principal therapeutic

[14] See the ATC classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) available at https://www.whocc.no/atc_ddd_index/. Further details on the classification system can also be found at https://www.whocc.no/atc/structure_and_principles/ (accessed June 2020).

[15] For information on some stakeholder-led databases, refer to Annex 1 of https://www.pgeu.eu/wp-content/uploads/2019/03/170201E-Supply-chain-Statement-on-Information-on-Med-Short.pdf (accessed December 2020).

[16] Data presented here are as-reported. There may be complex commercial incentives influencing reporting by some stakeholders, the exploration of which is beyond the scope of this paper.

[17] Germany, Spain, Italy, Denmark, Sweden, Norway, Hungary, Lithuania, Austria, Belgium, Ireland

classes affected by unresolved shortages between 1st January 2019 and 31st August 2019 were consistent between countries. ATC C (cardiovascular) was the most prevalent in all 11 countries, accounting for 27% of all stock keeping units across all countries, followed by ATC N (nervous system) with 25%. It was also found that shortages in different countries were not driven by the same products or manufacturers (ibid.)

23. However, **shortages have primarily been examined at country level.** In 2019, a scoping study was published with a qualitative review of the literature, based on 56 studies in total, covering 19 countries, 11 of which are OECD countries, and 2 regions (Europe and Latin America) (Acosta et al., 2019[4]). In this article, authors found that shortages **of medicines identified as essential by the respective health systems, including active pharmaceutical ingredients in injectable cancer medicines, antibiotics and anaesthetics, were a growing concern overall in North America, Europe, Asia and South America**. Shortages were found to also affect other classes of products (mainly injectables), including nutrition and electrolytes, enzyme replacement, radiopharmaceuticals and antibiotics. Another study found that the most commonly reported medicines in shortage in France between 2012 and 2018 were antimicrobials for systemic use (18%), followed by nervous and cardiovascular system products and anti-cancer and immunomodulatory agents (17.5%, 12.5% and 10.4% respectively) (Benhabib et al., 2020[13]). Trends in therapeutic classes remained similar over time.

24. **Shortages have also been reported at hospital level**. For example, the European Association of Hospital Pharmacists (EAHP) surveyed European hospital pharmacists on the shortage situation in their countries in 2014, 2018, and 2019 (Miljković et al., 2019[14]; Miljković et al., 2020[15]). The proportion of hospital pharmacists reporting shortages as a problem has increased over time, from 86% in 2014, to 95% in 2019. **Reported shortages in some medicine groups were more frequent over time**. In all three years, **antimicrobials were the most frequently reported** by hospital pharmacists (63%, 2019; 77%, 2018; 57%, 2014). After antimicrobials, the most commonly reported shortages in 2019 were oncology medicines (47%), followed by anaesthetic agents (39%). While the proportion of reported oncology medicine shortages dropped between 2014 and 2018 – cited by the authors as possibly due to the introduction of biosimilars - it increased again in 2019 (47%, 2019; 39%, 2018; 54%, 2014). The proportion of shortages reported for preventative medicines, i.e. vaccines, more than doubled between 2014 and 2018 (43%, 2018; 20%, 2014), but has since decreased. (Miljković et al., 2019[14]). Furthermore, a point prevalence survey of Australian hospitals on 4 April 2017 found 1577 entries of reported shortages, most frequently for antimicrobials (20%), followed by anaesthetics/analgesia (12%), cardiology (10%), endocrinology (10%), chemotherapy (9.5%) and neurology (9%) (SHPA, 2017[10]).

25. **Shortages at the community pharmacy level have also been studied**. In 2019 and 2020, the Pharmaceutical Group of the European Union (PGEU, representing community pharmacies) published results of an annual survey on medicine shortages (PGEU, 2019[16]; PGEU, 2020[17]). All responding countries (24 nationally representative institutions in 2019; 26 in 2020) reported having experienced medicine shortages[18] in community pharmacies in the past 12 months, and **the vast majority of countries indicated that the situation was worse compared to the previous year (87% in 2019 compared to 2018; 65% in 2020 compared to 2019)**. All classes of medicines were affected by medicine shortages in community pharmacies and, in the majority of responding countries (67% in 2019; 65% in 2020), over 200 medicines were listed as in short supply at the time of survey completion. In 2019, cardiovascular medicines were reported to have been in short supply in 92% of responding countries, followed by vaccines (88%), nervous system (84%) and respiratory system (84%) medicines (PGEU, 2019[16]). In the United States' context, a 2017 survey of around 300 pharmacy directors, managers and purchasing agents found shortages in all treatment categories, with 87% of respondents reporting shortages in emergency care,

[18] For the purposes of the PGEU survey, a medicine shortage was defined as "every (temporary) inability for a community or hospital pharmacy to supply patients with the medicinal product requested as a result of factors beyond their control…" (PGEU, 2020[17])

85% in anaesthetic care, 81% in pain management, 71% in infectious disease treatment and 68% in cardiovascular care (U.S. FDA, 2019[18]).

26. Overall, **shortages mainly concerned older, off-patent products**. For example, according to a 2019 FDA report, of 163 medicines that went into shortage during the period 2013 to 2017; 63% of the sample were injectable medicines, 67% had a generic product on the market, and they were also older drugs (U.S. FDA, 2019[18]). In France, of 3530 pharmaceutical products with reported national shortage between 2012 and 2018, 63.4% were old products, 62.8% with a national marketing authorisation (rather than an EU-wide), in both injectable and oral forms (47.5% and 43.3%, respectively) (Benhabib et al., 2020[13]). As per the aforementioned analysis by IQVIA, the majority of shortages were for generic products with alternative manufacturers (Troein et al., 2020[5]). Only 1% to 8% of the stock keeping units reported in shortage were for products with patent protection (i.e. no direct alternative), 5% to 40% for original products that were no longer patent-protected, and more than half (52% to 79%) for generic products (ibid.)

3. The magnitude of the problem in OECD countries

27. As seen in Section 2. , major differences in the way shortages are reported make cross-country comparisons very challenging to interpret. Despite this caveat, a group of national databases were identified and aggregated to provide a high-level assessment of the situation in OECD countries. The main objectives of this analysis were not to compare numbers of notifications across countries (which is presented in Section 3.1), but to identify 1) the key therapeutic areas affected by shortages (Section 3.2), 2) whether shortages were predominantly country-specific or cross-national (Section 3.3) and 3) the type of product concerned (e.g. older, off-patent or more recent products) (Section 3.3).

28. The analysis below covers 14 OECD countries: Austria, Belgium, Canada, Estonia, France, Germany, Hungary, Iceland, Latvia, Norway, Portugal, Sweden, Switzerland and the United States. The data for these countries were either publicly available or shared with the Secretariat by national authorities. All notifications in the databases for human medicines with a shortage start date (or anticipated start date) between 01 January 2017 and 31 December 2019 were included[19]. A three-year period was selected, on the assumption that a problem in the supply chain that is likely to impact several countries, could affect them at different times. See Box 3.1 for information on interpretation of the data presented and Supplementary Material 1 for further details on methods and analysis.

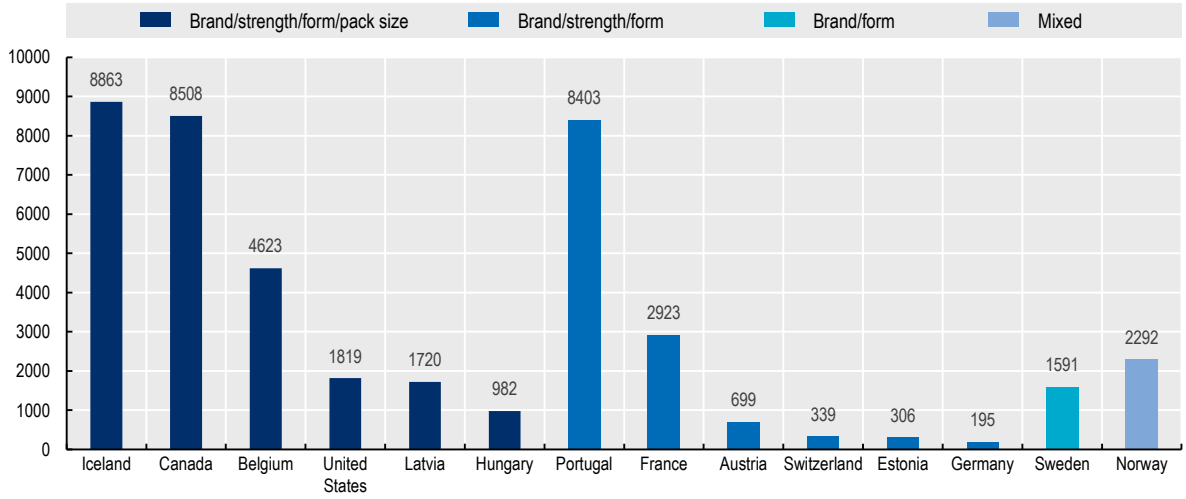
3.1. Shortage notifications increased by 60% between 2017 and 2019

29. Between 2017 and 2019, more than 46 000 shortage notifications were made in the 14 studied countries, with variation across countries likely reflecting differences in notification practices and reporting (see Box 3.1). Despite these caveats, trends are generally similar across countries. **The number of notifications per country ranged from 195 in Germany to 8 863 in Iceland** (Figure 3.1). The high number for Iceland likely reflects that the data were notifications from wholesalers/distributors of products that may be temporarily unavailable in pharmacy stores, rather than those expected or current shortages notified by MAHs to the competent authority like for the other countries analysed. This exemplifies that registries held by different stakeholders meet different needs and paint a different picture. Other variations between countries likely reflect both differences in notification practices but also the occurrence of shortages at national levels. As mentioned in Box 3.1, some countries such as Belgium, Iceland and Canada, report shortages at a very detailed level (pack-size) while others report by brand/strength/form (see Table 6 in Supplementary Material 1). These various approaches artificially inflate differences across countries since the same shortage information could lead to one or several notifications depending on the manner of reporting. In addition, the numbers may reflect differences in enforcement, and may be inflated in those countries that apply sanctions (e.g. Canada, Portugal). On the other hand, notifications may be underestimated in some countries, for example, if reports are only published for medicines considered important/essential (France, Switzerland, United States), or discontinued products are not maintained in

[19] The Estonian database did not capture notification dates, however, in light of the limited number of notifications and the time of extraction of the data (February 2020) the decision was taken to include it in the analysis.

the notification database used for analysis (e.g. Austria, Germany, Sweden). In a few countries, notification of shortages is, or was previously (e.g. Austria and Germany until end March 2020), only voluntary.

Figure 3.1. Total number of notifications by country (2017-2019)



Note: Colour-coded by shortage notification "units". For example, in the Canadian data there is one notification row per brand/strength/form/pack size. Data definition and comparability (including caveats) is summarised in Box 3.1and in Table 6, Supplementary Material 1.
Source: Authors based on national data. See Table 6, Supplementary Material 1, for country data sources.

30. **Across the 14 OECD countries included in the analysis, the total number of notifications increased by 60% between 2017 and 2019, from close to 11 000 to more than 17 500**. Despite the differences in the methodology and data collection mentioned above, notifications increased in most countries, but ranged from a 0.43-fold decrease in Hungary, to a 35-fold increase in Sweden between 2017 and 2019. This overall increase has at least two explanations.

- First and foremost, all countries have strengthened and increased their monitoring of medicine shortages over the study period. Reporting has been made more detailed and exhaustive and there has been an increase in awareness of reporting requirements.
- Second, the number of medicine shortages has increased globally.

31. These data need, however, to be interpreted with caution. This analysis is based on shortage notifications, which also includes expected shortages, even if these do not materialise. This could potentially explain the discrepancy between the findings presented in this paper and those in other reports. An infographic published by the US FDA for example, shows that actual shortages of essential medicines have been decreasing since 2011 (U.S. FDA, 2019[19]).

Box 3.1. Definition and comparability of data from 14 OECD countries

The analysis covers 14 OECD countries: Austria, Belgium, Canada, Estonia, France, Germany, Hungary, Iceland, Latvia, Norway, Portugal, Sweden, Switzerland and the United States. Data were extracted from publicly available databases or those shared by national authorities. With the exception of Iceland, all databases were national (government-based) databases, predominantly comprising notifications from Marketing Authorisation Holders (MAH). Notifications in these reporting systems may include both actual and anticipated shortages, and both temporary and permanent discontinuations (i.e. withdrawal from the market). All notifications for human medicines with a shortage start (or anticipated start date) between 01 January 2017 and 31 December 2019 were included in the analysis. See Supplementary Material 1, section "*OECD analysis of medicine shortage notifications across 14 OECD countries*" for further details on methods and analysis, and Table 6 for a summary comparison the of shortage notification data reviewed and associated caveats. Note that the databases differ in their classification of "units" of a shortage notification, hampering cross-country comparisons. Countries are grouped according to their "units" so as to highlight groups of countries for which the "units" are comparable.

- **[Belgium, Canada, Hungary, Iceland, Latvia, and the United States]** One notification row per pack size (i.e. per combination of brand/strength/form/pack size). For these countries, a shortage affecting different pack sizes for the same combination of brand/strength/form will lead to separate notifications.
- **[Austria, Estonia, France, Germany, Portugal and Switzerland]** One notification row per combination of brand/strength/form. For these countries, a shortage affecting two different posology for the same brand and routes of administration will lead to two separate notifications.
- **[Sweden]** One notification row for multiple strengths of a product (i.e. one notification per combination of brand/form).
- **[Norway]** The database structure changed over the period; in some cases there may be one notification row for brand/strength/form/pack size, and in others, per brand/form.

In addition, other differences in the data used for this analysis should be considered when interpreting the results. A non-exhaustive list is included below (see Table 6, Supplementary Material 1, for further details):

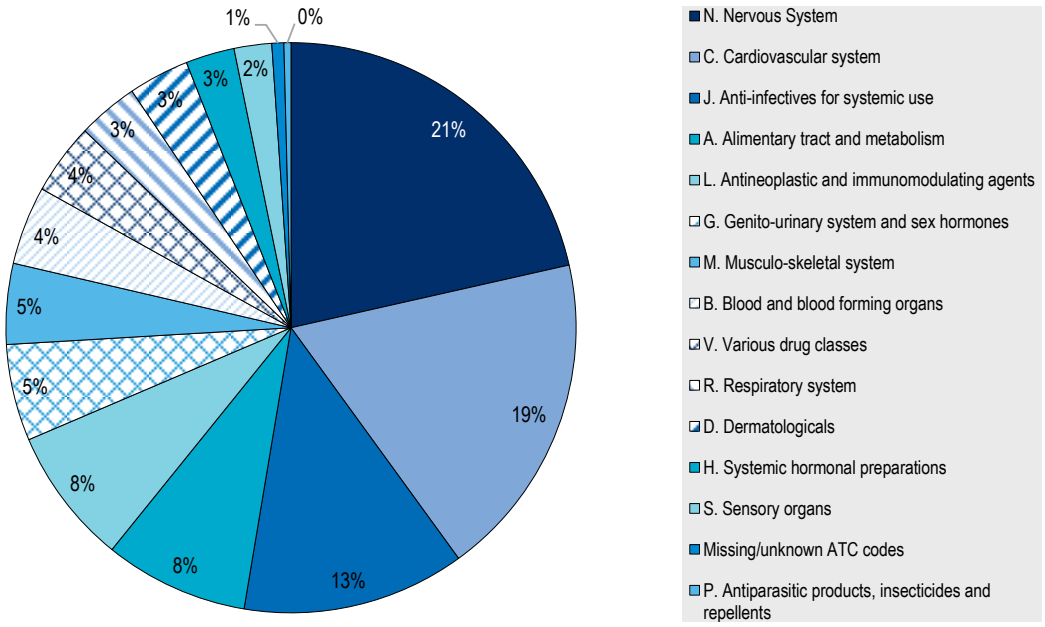
- **[Austria, Germany]** Data include voluntary notification by MAH during the study period.
- **[Canada]** Medicine can be affected by shortage more than once in a single reporting period.
- **[Estonia]** Data include current shortages as of 21 February 2020 (i.e. after the period of analysis defined for all other databases).
- **[Iceland]** Data include those products on the market which may temporarily not be in pharmacy stores (based on notifications from wholesalers/distributors and data compiled by the Icelandic Health Insurance).
- **[France, Switzerland, the United States]** Data include only a subset of products considered essential by their respective health care systems.
- **[Austria, Germany, Sweden]** Data do not include discontinued products (i.e. those withdrawn from the market).

Source: Authors based on sources cited in Supplementary Material 1.

3.2. More than half of all shortage notifications arise from three pharmaco-therapeutic areas

32. The analysis of the total number of notifications by Anatomical Therapeutic Classification (ATC)[20] level 1 confirms in part what has been reported in the literature so far as described in Section 2.4. When averaging the proportions across countries, **medicines targeting the nervous system (ATC group N) and cardiovascular drugs (ATC group C) were the most frequently subject to shortage notifications** (each accounting for around one-fifth on average). ATC group N includes among others: anaesthetics, analgesics, anti-convulsants, and treatments used in psychiatry such as antidepressants and anxiolytics. ATC group C covers all the treatments addressing issues such as hypertension, high cholesterol levels in the blood and problems with cardiac rhythm and heart function. **The third highest group of treatments subject to short supply notifications were anti-infective agents such as antibiotics, antivirals and vaccines** (ATC group J, 13% on average). These three ATC groups (N, C and J) represented more than half of the share of all notifications between 2017 and 2019 (Figure 3.2). It must be acknowledged that these are absolute data, and do not take into account the number of authorised medicines in each therapeutic class and marketed in each country. As such, it is possible that these findings over- or under-estimate the issue of shortages in some classes, when there may in fact just be more or less medicines marketed in some therapeutic classes than in others.

Figure 3.2. Medicines targeting the nervous system, cardiovascular system, and anti-infectives account for more than half of all shortage notifications in 14 OECD countries (2017-2019)



Note: Therapeutic areas are based on Anatomical Therapeutic Chemical (ATC) code level 1 groups. Data definition and comparability (including caveats) is summarised in Box 3.1 and in Table 6, Supplementary Material 1.
Source: Authors based on national data. See Table 6, Supplementary Material 1, for country data sources.

[20] See the ATC classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) available at https://www.whocc.no/atc_ddd_index/ (accessed June 2020). Further details on the classification system can also be found at https://www.whocc.no/atc/structure_and_principles/ (accessed June 2020).

33. The **distribution of shortage notifications by therapeutic area were not uniform across countries** (see Table 3.1). Nervous system treatments (ATC group N) accounted for between 11% of the total notifications in Switzerland to 34% in the United States, cardiovascular drugs (ATC group C) between 7% in Switzerland to 34% in Germany, and anti-infective agents (ATC group J) between 6% in the United States and 50% in Switzerland. Overall, these three pharmaco-therapeutic groups represented around 50% of the total notifications in all countries except Hungary (32%), Norway (45%) and Sweden (42%). Note that Norway and Sweden report notifications differently than other countries (cf. Box 3.1 and Table 6, Supplementary Material 1). Cross-country differences in the proportion of notifications by pharmaco-therapeutic class may be related to differences in notification requirements (see Section 2.). Indeed, in some first level ATC groups there might be more medicines considered as vital than in others, and this could have an influence on the distribution of notifications across ATC groups in countries only reporting shortages for vital medicines (see Section 2.). This may explain, for example, Switzerland's 50% of notifications on ATC group J. Furthermore, not all countries may have the same innovative medicines authorised, or some countries may use more of the same medicines than others due to their medical practices or guidelines.

Table 3.1. Share of notifications by therapeutic area were not uniform across countries (2017-2019)

	Anatomical Therapeutic Chemical (ATC) level-1 code														
	N	C	J	A	L	G	M	B	V	R	D	H	S	X	P
Country	Nervous system	Cardiovascular system	Anti-infectives for systemic use	Alimentary tract and metabolism	Antineoplastic & immunomodulating agents	Genito-urinary system & sex hormones	Musculo-skeletal system	Blood & blood forming organs	Various drug classes	Respiratory system	Dermatologicals	Systemic hormonal preparations	Sensory organs	Missing /unknown ATC codes	Antiparasitic products, insecticides & repellents
Austria	15%	21%	14%	9%	7%	9%	5%	4%	1%	4%	5%	2%	2%	3%	0%
Belgium	21%	23%	8%	8%	6%	10%	5%	2%	4%	4%	4%	2%	2%	0%	0%
Canada	28%	25%	8%	9%	5%	6%	4%	3%	2%	2%	4%	2%	2%	1%	0%
Estonia	18%	21%	10%	8%	12%	8%	6%	3%	0%	3%	5%	4%	2%	0%	0%
France	19%	20%	15%	7%	10%	3%	4%	9%	2%	2%	1%	4%	3%	1%	1%
Germany	24%	34%	10%	7%	6%	2%	3%	4%	1%	1%	1%	8%	1%	0%	0%
Hungary	13%	12%	7%	7%	7%	4%	4%	10%	27%	3%	2%	2%	1%	1%	0%
Iceland	27%	10%	10%	9%	7%	5%	4%	5%	3%	7%	5%	3%	4%	0%	1%
Latvia	20%	19%	10%	10%	8%	6%	6%	4%	2%	6%	4%	2%	4%	0%	0%
Norway	20%	14%	11%	12%	6%	7%	6%	4%	2%	6%	5%	3%	2%	1%	0%
Portugal	27%	25%	8%	7%	5%	6%	6%	3%	2%	3%	3%	1%	1%	3%	0%
Sweden	24%	9%	9%	9%	7%	10%	5%	6%	2%	5%	5%	3%	5%	0%	1%
Switzerland	11%	7%	50%	2%	20%	0%	1%	4%	4%	0%	0%	1%	1%	0%	0%
United States	34%	19%	6%	12%	4%	3%	5%	3%	5%	2%	3%	1%	2%	0%	1%

Note: Therapeutic areas are based on Anatomical Therapeutic Chemical (ATC) level-1 codes, ordered left to right according to the distribution across OECD countries seen in Figure 3.2. Graded colour scale from dark blue to light blue from highest to lowest proportion in each country. Data definition and comparability (including caveats) is summarised in Box 3.1 and in Table 6, Supplementary Material 1.
Source: Authors based on national data. See Table 6, Supplementary Material 1, for country data sources.

3.3. Shortage notifications of most active substances are made in more than one country

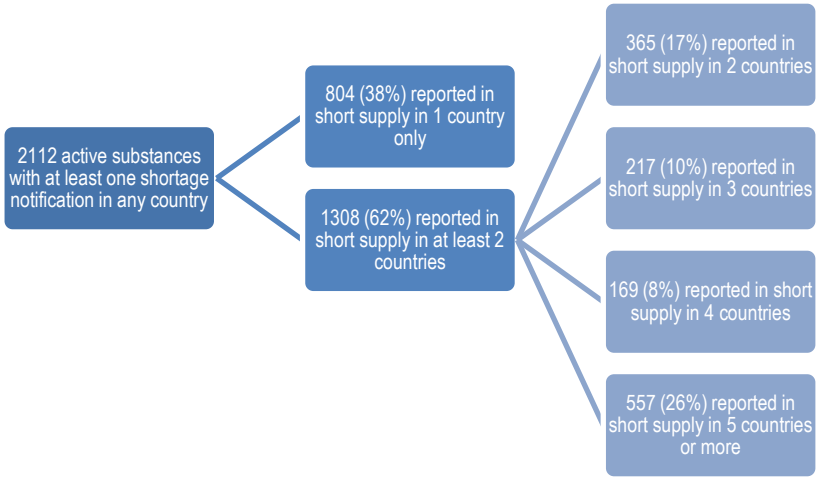
34. Even though more than half the total number of notifications were concentrated in three broad therapeutic areas (Figure 3.2), shortages affect products across the entire global pharmacopoeia. More

than 40% of the total number of active substances[21] listed in the WHOCC ATC classification index were subject to *at least one* shortage notification in the sample of countries analysed (2112 out of 5126 active substances listed in the 2020 ATC classification).

35. In **nearly two-thirds of cases, a shortage of a given active substance was notified in more than one country** during the analysis period. Of the active substances for which a shortage notification was reported in any country, more than 60% (1308 of 2112) were reported in at least 2 countries, and in some cases in as many as 13 (Figure 3.3). This proportion may yet be an underestimate, as some countries only report for medicines deemed essential to their healthcare systems, while others report on all shortages. However, it suggests that a substantial proportion of shortages are not country specific and may result from systemic issues rather than local factors.

36. A few active substances were subject to at least one shortage notification in almost all studied countries: 5 active substances were reported in shortage in 13 countries, 12 in 12 countries, and 27 in 11 countries (see below for further details). While this analysis did not consider a temporal component, *per se*, due to lack of data comparability, **this suggests that some shortages may have common root causes**.

Figure 3.3. Almost two thirds of active substances with shortage notifications were reported in shortage in at least 2 countries



Note: The figure can be interpreted as follows: e.g. 217 active substances were reported in short supply at least once in 3 different countries; i.e. 10% of the 2112 active substances with a shortage notification reported in any country were reported in 3 countries. Data definition and comparability (including caveats) is summarised in Box 3.1 and in Table 6, Supplementary Material 1.
Source: Authors based on national data. See Table 6, Supplementary Material 1, for country data sources.

37. Furthermore, on average, only 11% of the total number of active substances reported in short supply in countries were reported to be missing in this country only (see Table 7, Supplementary Material 1). This proportion varied from 3% (6 of 180 active substances) in Estonia to a maximum of 17% (135 of 814) in Canada. No major differences across countries were found in the types of products subject to shortage notification in one country only.

38. A closer analysis of the active substances with shortage notifications in the majority of the countries (11, 12 and 13 countries) provides a complementary picture of the situation (see Table 8, Supplementary Material 1). One-third of these active substances were anti-infective agents (14 out of 44), mainly antibiotics

[21] Analysed at the ATC-5 level.

and vaccines. About 20% were anticancer agents (9 out of 44), mainly old products used in standard chemotherapy protocols and 15% were active substances belonging to the ATC group N (7 out of 44, 15% of the total), including common analgesics and anti-convulsants.

39. **All of these active substances with shortage notifications in more than 11 countries, except the vaccines, are older molecules no longer protected by patents.** Importantly, more than half (23 of 44) are included in the 21st WHO *Model List of Essential Medicines* (EML),[22] with a further eight in the complementary list. One antibiotic (linezolid) is classified as one of the 22 "reserve" antibiotics according to the 2019 WHO Access, Watch, Reserve (AWaRe) classification list of antibiotics.[23] This means that it is reserved for infections due to multi-drug resistant organisms and should be used only as a "last resort". Another seven antibiotics reported in short supply are high priority agents with high resistance potential.

40. The **20 active substances with the highest number of notifications across all countries were also all older molecules, no longer protected by patents** (Table 9, Supplementary Material 1). Valsartan, used in the treatment of high blood pressure and heart failure, was first, with a total of 411 notifications in 12 countries over the three years of analysis[24], followed by pregabalin, for neuropathic pain and seizures, on par with quetiapine, an antipsychotic (385 notifications in 10 countries each). Half of the 20 active substances with the highest number of notifications belonged to the ATC group N (nervous system) and 7 were cardiovascular medicines. No anti-infective (ATC group J) was part of the 20 active substances most frequently reported in short supply. Note that a high number of shortage notifications for one active substance may reflect that there are multiple different brands, forms or pack sizes on the market, leading to more notifications if, for example, there is an issue with the availability of the API. However, this does not necessarily imply an equivalent pressure on availability of treatment for patients (see Box 3.2).

Box 3.2. A shortage notification does not necessarily imply a shortage that impacts patients

While shortages can have a direct impact on health service delivery and ultimately on patients' health outcomes, it is difficult to quantify the extent to which shortage notifications in the OECD analysis led to a serious public health issue in the studied countries (i.e. direct impact on patients/health care professionals). A given shortage notification for an active substance does not necessarily constitute a shortage that impacts patients. This depends, for example, on the availability of appropriate alternatives in sufficient quantities e.g. another pack size / strength / dosage form / generic version of the same active substance, or the existence of a therapeutic alternative in the same or a different therapeutic class. The impact on patients also depends on the nature and seriousness of the condition being treated. Lastly, the importance of a given product may vary from country to country as the degree of "criticality" may be country specific.

Source. Authors.

[22] WHO 21st Model List of Essential Medicines available at https://www.who.int/medicines/publications/essentialmedicines/en/ (accessed 01 June 2020).

[23] WHO AWaRE classification of antibiotics available at https://www.who.int/news/item/01-10-2019-who-releases-the-2019-aware-classification-antibiotics (accessed 01 June 2020).

[24] The high number of notifications for valsartan and other angiotensin II receptor antagonists (i.e. 'sartans') over this period is largely the result of regulatory actions that followed the identification in 2018 of certain nitrosamine impurities, including N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), considered probable human carcinogens, in some batches of active pharmaceutical ingredients (APIs) of these medicines. For further information see https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities (accessed 01 June 2020).

4. Drivers of medicine shortages

41. A number of studies have explored the reasons for medicine shortages as reported by marketing authorisation holders (MAHs), and have found that they are not comparable across OECD countries (see for example (Acosta et al., 2019[4]; Troein et al., 2020[5]). Reporting to national or regional regulatory authorities is highly heterogeneous, and in order to gain insights into the nature, extent and sources of shortages, Section 4.1 proposes a conceptual framework and taxonomy. Using this taxonomy, the following sections explore some of the supply-side drivers of shortages, including logistics and distribution problems (Section 4.2), manufacturing and quality issues (Section 4.3), and some of the commercial factors and policy settings that influence them (Section 4.4).

4.1. A conceptual framework and functional taxonomy are needed for effective root cause analysis

42. The complex nature of medicine shortages and lack of sufficient data complicate root cause analysis. Prior analyses of the causes of shortages have drawn on notification data, but the data remain insufficient to draw any strong conclusions. In many countries, MAHs are required to report the reasons for expected or current shortages, at the time of notification. However, with the exception of countries such as the United States[25] and Belgium, reporting systems generally allow the use of free text, making compilation of the data challenging. The extent to which this information is made public also varies between countries (see row on causes in Table 5, Supplementary Material 1). Troien et al (2020[5]) identified that the situation is complex, with a number of underlying problems including, but not limited to, variable shortage definitions, low data quality, use of prior notification lists, tendering system pressure, lack of information around parallel trade, and involvement of multiple stakeholder perspectives. As stated by Troien et al., the reasons reported by MAHs in shortage notifications to national or regional regulatory authorities are generally not comparable and do not provide significant insight into the root causes of shortages (Troien et al., 2020[5]).

43. As highlighted by Troien et al. (2020[5]), previous work into this area is also dependent on the stakeholder perspective when publishing reported causes. For example, in 2019, a group of seven "Supply chain stakeholders" involved in the European market published a position paper on the root causes of shortages. The group agreed to define three broad categories of root causes of shortages: "manufacturing and quality issues", "economic-related issues" and "supply chain issues" (with subcategories including manufacturing lag times, Good Manufacturing Practice (GMP) issues, pricing mechanisms, cost-containment measures, supply quotas and parallel export, etc.).[26] Despite showing a broad agreement

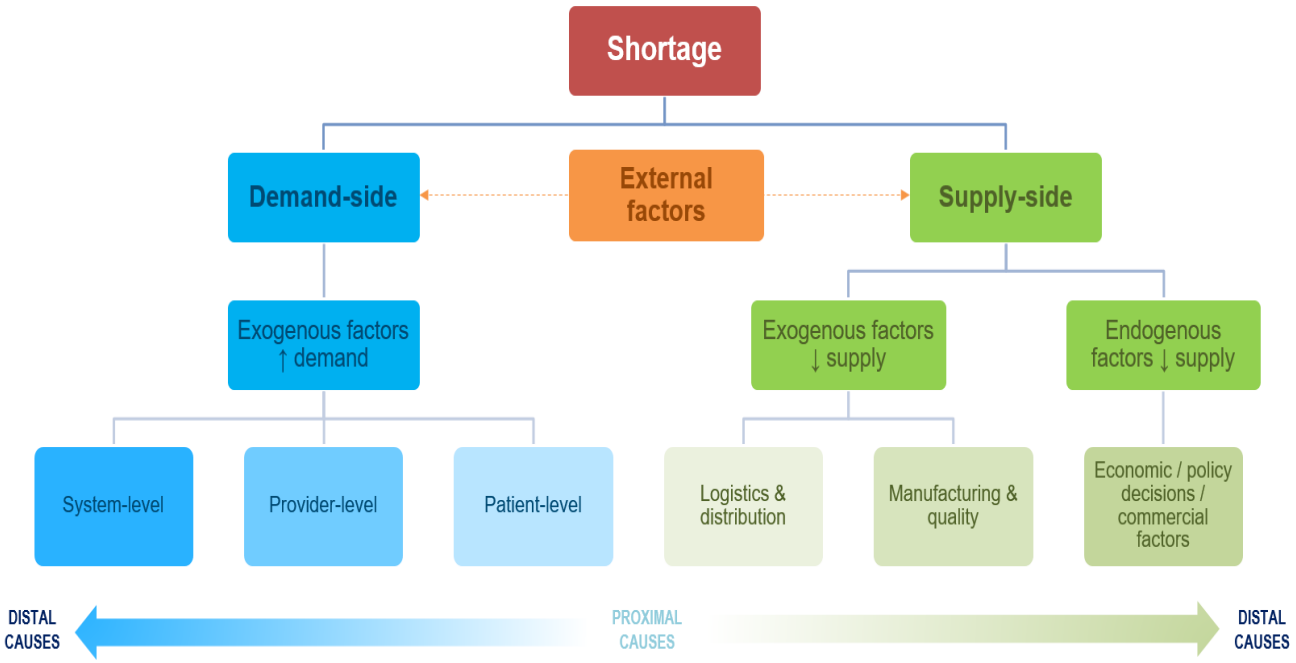
[25] According to the US Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 (21 USC 356e.), the drug shortage list should include the following reasons for a shortage1: (A) Requirements related to complying with good manufacturing practices. (B) Regulatory delay (C) Shortage of an active ingredient. (D) Shortage of an inactive ingredient component. (E) Discontinuation of the manufacture of the drug. (F) Delay in shipping of the drug. (G) Demand increase for the drug. See https://www.govinfo.gov/content/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf (accessed 01 June 2020).

[26] See http://girp.eu/sites/default/files/documents/addressing_the_root_causes_of_medicines_shortages_-_eu_supply_chain_stakeholders_views_on_root_causes_and_solutions.pdf, published 6 December 2019 (accessed

across involved parties, this position paper, reveals some ambiguities that are quite specific to the European Economic Area (EEA). The group considered causes of unavailability of medicines, including for products which are not yet authorised in every national market and products which are authorised but not yet launched in some countries. This does not match with the generally accepted definition of shortages (by which only medicines already approved and marketed can be in shortage) but coincides with concerns expressed by the European Medicines Aagency (EMA) and the Heads of Medicines Agencies (HMAs) about the availability of medicines authorised but not yet launched in all EU countries. Also, in this region, marketing authorisation can be granted for all countries of the EU, Norway and Iceland at the same time, and medicines can be purchased in one country by a wholesaler to be exported in another country (a practice often referred to as “parallel trade”).

44. Despite the above noted challenges, and while a number of additional elements need to be considered when assessing the drivers of medicine shortages (see Box 4.1), the potential causes of medicine shortages may be grouped conceptually as due to: demand-side vs supply-side factors; distal vs proximal causes; and endogenous vs exogenous factors. This classification schema is presented in Figure 4.1, and elaborated in Table A A.1.

Figure 4.1. Complex nature of shortages complicates root cause analysis



Source: Authors, based on review of the available literature, including (Acosta et al., 2019[4]; Benhabib et al., 2020[13]; U.S. FDA, 2019[18]; Bogaert et al., 2015[20]; De Weerdt et al., 2015[21]; Pauwels et al., 2014[22]; Musazzi, Di Giorgio and Minghetti, 2020[23]) and http://girp.eu/sites/default/files/documents/addressing_the_root_causes_of_medicines_shortages_-_eu_supply_chain_stakeholders_views_on_root_causes_and_solutions.pdf , published 6 December 2019 (accessed June 2020).

June 2020). This paper was developed and agreed on by the Association of the European Self-Medication Industry (AESGP), The European Association of Euro-Pharmaceutical Companies (EAEPC), The European Industrial Pharmacists Group (EIPG), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Healthcare Distribution Association (GIRP), Medicines for Europe, and Vaccines for Europe.

Box 4.1. Points to consider in assessing the drivers of medicine shortages

When reviewing available information and conceptualising causes of medicine shortages[1], it is important to consider the following elements:

- **Perspective:** perceptions of the causes of shortages may vary, not only between stakeholders, but also from country to country.
- **Definition:** perceptions of the causes of shortages may vary according to the specific shortage definition used (see also Box 2.1).
- **Nature (and duration) of shortage:** temporary supply disruptions or permanent product discontinuation (i.e. withdrawal).
- **Position of the product in its life-cycle:** e.g. on-patent; single-source, or subject to generic competition (i.e. off-patent; multi-source).
- **Stage of the supply chain where the disruption occurs** (which may differ from where it is reported): supply of raw materials, manufacturing (API, FPP), transportation, distribution, retail / dispensing.
- **Reporting country features:** producer, non-producer, EU single market, coverage/pricing/procurement processes.
- **Nature of manufacturing/production process for the product:** sterile injectables, vaccines, topical preparations, oral formulations etc.
- **Structure of supply network:** number; concentration, diversification of manufacturing sites

Note: API active pharmaceutical ingredient, FPP finished pharmaceutical product. 1. These refer to medicine shortages at the individual product level, for a product that is already authorised and marketed but supply is unable to meet national demand.
Source: Authors based on information reviewed.

45. **Exogenous demand-side factors** include acute (temporary) or long-term (persistent) changes in health care needs, and occur proximally at the level of the patient, or more distally at the level of the provider or health system. Examples of underlying causes of increased demand include outbreaks of disease, panic-buying, stockpiling (at any level of the supply chain), shortage of products with similar indication(s), changes in prescribing guidelines or diagnostic criteria, variations in coverage/pricing and procurement, GDP growth stimulating demand; and external factors such as epidemics/pandemics or natural or human-induced disaster.

46. **Proximate supply-side factors** include exogenous factors leading to reductions in supply that may be broadly categorised into i) logistics and distribution issues, and ii) manufacturing and quality issues. Logistics and distribution problems may include transport disruptions, logistical inefficiencies in distribution by wholesalers or manufacturers, trader barriers etc. Manufacturing and quality problems include production quality issues or defects in any component of a product; shortage of inputs; inventory and storage practices; temporary or permanent suspension of production due to e.g technical issue with production or non-compliance with GMP, or manufacturing site closure or relocation. Health emergencies or natural or human-induced disasters may also contribute to issues with production and distribution of medicines.

47. **Distal causes of supply-side shortages, in particular for off-patent products,** may lie in the commercial decisions of MAHs or the policy settings that influence them (i.e. endogenous factors that lead to reductions in supply). For example, a lack of appropriate incentives to produce less profitable drugs may influence decisions to suspend production, close or relocate manufacturing sites, or limit manufacturing capacity. Global portfolio management decisions may be driven by declining profitability (e.g. due to

increasing price competition, declining market share, change of clinical protocols, increasing transaction costs, loss of coverage or reimbursement); comparatively poor profitability (e.g. where a product is less profitable than other product lines) or internal competition (e.g. where a product competes with and compromises the profitability of other company products). A decision to restrict sales of a product in a given country may also be a response to poor sales performance, or intended to reduce the risk of parallel export or arbitrage. In some cases, commercial decisions may also drive production quality issues, for example, decisions not to invest in quality systems, upgrade production sites for GMP compliance, or respond to changes in environmental or safety regulation. Inability of supply to meet demand may also result from decisions to concentrate or aggregate manufacturing (i.e. in a small number of manufacturing sites), on reliance on a sole active pharmaceutical ingredient (API) supplier, or on an increase in the number of products on available production lines.

4.2. Complex supply chains can create logistics and distribution challenges, but can also contribute to maintaining supply

48. As seen in Figure 2.1, pharmaceutical supply chains are often highly complex, involving multiple steps and stakeholders, and frequently distributed across multiple countries and/or locations. Thus, even absent manufacturing issues, logistics and distribution challenges can give rise to delivery delays or disruptions, thereby driving shortages.

49. In fact, internationalisation of medicine supply chains is often singled out in policy debates as a factor increasing risks to the supply of medicines, however evidence is lacking (Section 4.2.1). Moreover, internationally disruptive events such as COVID-19 have shown that trade barriers can contribute to supply disruptions, and that reducing these is essential to maintaining supply internationally (Section 4.2.2). As no one country is able to produce all the necessary components and medicines for its population, internationalisation could be seen as a means of reducing risks through diversification of supply channels.

4.2.1. The global supply chain of medicines is highly complex

50. Internationalisation of the entire value-chain is often singled out in policy debates as increasing the vulnerability of global medicine supplies to internationally disruptive events such as conflict or trade restrictions. However, concrete evidence is lacking. The term "*internationalisation of the value chain"* itself refers to the reliance on multiple countries for the production of all necessary medicines and components, but also entails other characteristics linked to the globalisation of supply chains (e.g. zero stock policies).

51. Measuring international trade flows can offer some insights into the extent of such interdependencies (even though the data are not sufficiently granular to draw strong conclusions). Evidence from 2018 trade flows data indicates a high degree of interdependence across countries for medicines supply (see Supplementary Material 2 for details on methods and analysis). *All* countries import both medicines for final consumption and pharmaceutical intermediates, and the relative proportions of these two categories offer a broad picture of the role of each country in the value chain. Some countries import a high proportion of intermediate goods, which means that they are likely to have a more significant role in the production process. For example, intermediate goods accounted for the largest part of the value of imports for Ireland (77%) and India (74%), followed by Austria (64%), Brazil (57%), and Indonesia (56%). By contrast, the United States, Switzerland, China and Japan imported a higher share of finished products (around 60%) in value[27]. In addition, about 28% of products imported in the United States came from Mexico and about 18% from India, followed by Germany, Canada and Italy. EU countries mainly import

[27] Trade flows in value, however, only partially reflect country interdependence as prices vary greatly, and trade flows of quantities of pharmaceutical products, as collected by customs authorities, are more informative.

products from other European countries (including Switzerland) (Table 4.1). Box 4.2 provides a more detailed analysis for one category of antibiotics, penicillins.

52. While measuring international trade flows can give a glimpse into the degree of inter-country dependency, they do not necessarily provide a comprehensive picture of international trade. For example, the value of production from other contributors may not be reflected in the data as the "country of origin" recorded for imports represents only the last country in the production chain[28]. Furthermore, understanding the extent of interdependence in medicines' supply, goes beyond information on imports of finished products and would require more detailed analyses. In practice, the concentration of production may constitute a greater risk for supply than the internationalisation of the supply chain *per se* (see Section 4.3.2). **Internationalisation should also be seen as a means of reducing shortages through diversification of supply.**

Table 4.1. Main countries of import for the 5 biggest importers of finished medicines in 2018

Category HS 3004, quantities in kg, and country share of reporting country imports for top 5 partner countries

Ranking	Country	Total quantities imported	Partner 1	Partner 2	Partner 3	Partner 4	Partner 5
1	USA	World	Mexico	India	Germany	Canada	Italy
		440,270,592	27.9%	18.1%	10.0%	8.9%	5.4%
2	Germany	World	France	Spain	Italy	Switzerland	Belgium
		292,367,936	22.1%	12.0%	10.1%	9.8%	7.1%
3	Belgium	World	Ireland	United Kingdom	France	Germany	Netherlands
		273,573,216	22.6%	16.8%	13.3%	11.3%	9.4%
4	United Kingdom	World	France	Germany	India	Ireland	Italy
		219,260,800	20.0%	14.5%	10.7%	9.3%	6.8%
5	Russia	World	Germany	France	India	Belarus	Bulgaria
		144,513,840	17.5%	10.6%	8.8%	7.8%	4.7%

Note: Category HS 3004 refers to finished pharmaceutical products prepared for retail sales (3004) classified according to the Harmonized Commodity Description and Coding System (HS) version 5, 2017. Reporting country refers to the geographical entity reporting import of a given product. Partner country refers to the origin of the import.
Source: UN Comtrade Database, Data extracted between February and May 2020.

[28] For further insights and details see the trilateral study by the World Health Organization (WHO), World Intellectual Property Organization (WIPO) and World Trade Organization (WTO) on *Promoting Access to Medical Technologies and Innovation: Intersections between public health, intellectual property and trade; 2nd edition, July 2020* available at https://www.wipo.int/edocs/pubdocs/en/wipo_pub_628_2020.pdf (last accessed 30 November 2021).

Box 4.2. Trade statistics suggest production of penicillins and their derivatives originates in few countries, 2018

Trade movements for one category of antibiotics, penicillins, were examined using 2018 import data on chemicals used in their production, as well as on intermediate and finished products (see Table 1, Supplementary Material 2 for further details). Note that this analysis looks at trade data, and therefore does not take into account the quantity of domestic inputs used in the production of penicillins.

In 2018, India was by far the biggest importer of basic products used as inputs for the production of penicillins, with almost 20,000 tons of ingredients, 96% of which came from China. Quantities imported by the next highest reporting country, Italy, were lower by a factor of 5 and almost three quarters of them came from European countries (63% from Ireland and 9% from the Netherlands). The United Kingdom, ranking 4th, imported 74% of these products from Singapore, and France, ranking 7th, imported 50.8% from the same country. China was the first partner country for 7 of the top 10 importers, including the United States and Spain.

Imports of medicines containing penicillins, streptomycins or their derivatives which were not packaged for retail sale were less concentrated in the Top 10 importers. Indonesia was the largest importer, with more than 900 tons, half of which came from Bulgaria and one quarter from Brazil. Myanmar ranked second, with about 426 tons, of which two thirds came from Thailand. Turkey ranked third, with almost 85% of quantities imported coming from the United Kingdom.

Finally, imports of finished antibiotics containing penicillins, streptomycins or their derivatives, packaged for retail sale were the highest in the United States, with almost 8 350 tons. These imports came from Canada (21.6%), followed by India, Italy, Portugal and Slovenia, with the top 5 partner countries accounting for 70% of imports. European countries mainly imported these antibiotics from other European countries, except the United Kingdom, where almost 20% were imported from India.

Source: UN Comtrade Database, Data extracted between February and May 2020. See Table 1 in Supplementary Material 2 for details.

4.2.2. Trade barriers can increase the vulnerability of the supply chain

53. The COVID-19 pandemic offers an eloquent example of how trade barriers can affect supply of medicines. Indeed, COVID-19 presented a unique circumstance during which demand for critical medicines surged substantially worldwide, particularly early on in the crisis. Specifically, the demand for medicines used in intensive care units increased, including intravenous anaesthetic agents, antibiotics, muscle relaxants, resuscitation medicines; as well as medical oxygen. Increased demand for other putative and actual COVID-19 treatments also adversely affected their availability to patients requiring them for approved indications. Additionally, panic-buying and stockpiling of over-the-counter painkillers in reaction to the pandemic were commonly observed in countries (European Commission, 2020[24]).

54. Coupled with increasing demand, early in the pandemic saw countries across the world entering lockdowns, with disruptions in transport and logistics adversely affecting the movement of goods across borders. Several governments enacted temporary restrictive trade measures of vital medical supplies, including prescription medicines (OECD, 2020[25]; OECD, 2020[26]). As at the end of April 2020, medicines accounted for around 6% of total export restrictions introduced in relation to COVID-19 (OECD, 2020[25]). The measures imposed for medicines included **export bans** (i.e. entirely prohibiting exports or parallel exports) and **new licencing requirements** (i.e. new requirements for obtaining export licenses specifying which exporters could sell products abroad, limiting export quantities, and increasing the complexity and cost of procedures). Restrictions were placed on products used in the direct management of COVID-19 in

hospitalised patients, as well as those used in the general management of these patients, but also pertained to other medicines not related to care for COVID-19[29].

55. Restrictive measures such as these can not only contribute to scarcity in international markets, but also raise prices and reduce availability in non-producing countries. As seen in Section 4.2.1, no country is self-sufficient in the production of all the necessary medicines and their constituents, including those used to combat COVID-19, and **trade is an essential tool to increase availability internationally**.

56. In the EU context, parallel trade and restrictions on exports, i.e. quotas on national supply adopted by MAHs or export limitations introduced by countries in order to prevent parallel trade, have been cited as possible root causes of shortages. The association representing parallel traders notes however, that between 2010 and 2018, parallel trade has remained quite stable, at a value of around EUR 5.5 billion per year in current prices, and has actually decreased as a share of total sales of medicines in the European Union, from 3.7% to 2.9% (Aguiar and Ernest, 2020[27]). Although this does not evidence that parallel trade (and measures adopted to prevent it) has no impact on shortages, there is no obvious relationship between increases in the prevalence shortages observed in most European countries and trends in parallel trade.

4.3. Manufacturing and quality issues are frequently cited as a cause of shortages

57. Available information indicates that the majority of shortages are reported by MAHs to be due to manufacturing and quality issues. Section 4.3.1 explores quality issues, which may arise at the level of the manufacturing facility (leading to suspension or closure of an entire facility), or at the level of a specific production process in a given facility (leading to an issue with a specific batch of product). Section 4.3.2 looks at another frequently discussed issue with regard to manufacturing of medicines: the concentration or limited availability of manufacturing facilities to produce certain categories of medicines. This is seen as a possible additional source of vulnerability for supply chains even though its effect is difficult to evaluate based on available information.

4.3.1. Production processes can be a source of vulnerability

58. When information is available, manufacturing and quality issues are frequently reported as a cause of shortages. In the United States, for example, the Food and Drug Administration (FDA) analysed the reasons of shortages of 163 medicines reported between 2013 and 2017, based on MAH declarations. In almost two-thirds of cases (62%), quality issues, which include both defects in manufacturing and in the product/material, were at the origin of the shortage. Other reasons included: increased demand (12%), natural disaster (5%), and discontinuation of production (3%), but in 18% of cases, the reason was unknown (U.S. FDA, 2019[18]).

59. A 2020 study from France classified causes of shortages into five broad categories: (1) manufacturing issues, including at the early stage of manufacturing or packaging of the final product; (2) material issues, i.e. a defect in raw materials, excipients, packaging and semi-finished, or bulk pharmaceuticals; (3) pharmaceutical market, or the difficulty of the operator to purchase products, including insufficient production capacity; (4) regulatory issues e.g. a new regulation directly contributing to a delay in marketing; and (5) inventory and storage practices (e.g. stock errors or inappropriate management of

[29] For more information, see the World Trade Organization (WTO), International Trade Center (ITC) and World Customs Organization (WCO) websites. See also https://www.wto.org/english/tratop_e/covid19_e/trade_related_goods_measure_e.htm (accessed 10 July 2020), https://www.wto.org/english/tratop_e/covid19_e/notifications_e.htm (accessed 16 July 2020), https://macmap.org/en/covid19 (accessed 30 June 2020), and http://www.wcoomd.org/en/topics/facilitation/activities-and-programmes/natural-disaster/coronavirus.aspx (accessed 22 July 2020).

expiry dates) (Benhabib et al., 2020[13]). Similar to the United States, manufacturing and material issues together accounted for about 60% of all shortages each year during the observed period between 2012 and 2018.

60. In 2019, the European Healthcare Distribution Association (GIRP) reviewed websites of 12 national medicines agencies[30], and despite a lack of standardisation in reporting, estimated that more than 60% of shortage incidents were the result of manufacturing or quality related issues, with 27% arising due to marketing and commercialisation issues. The review also found that parallel trade, which is often claimed to be a significant cause of shortages in some countries, was not explicitly cited as a root cause in any of the notification databases reviewed. Moreover, while parallel trade was cited as a root cause for shortages in a report by the Spanish medicines agency AEMPS, it was noted to have declined from 2% in 2018 to 0.2% in 2019 (GIRP, 2019[28]).

61. In practice, the quality of manufacturing processes relies on adherence to guidelines, and is subject to inspection by regulatory authorities. While regulatory agencies attempt to monitor compliance with Good GMP in production sites of medicines with marketing authorisation in their jurisdictions, in reality this is only possible with some degree of international collaboration. For example, an International Active Pharmaceutical Ingredient Inspection Programme, designed to promote international collaboration and information sharing on GMP inspections of API manufacturers, was launched in 2008 by EMA and its European and international partners, and has been operational since 2011. The Programme involves nine institutions, mostly regulatory agencies from Europe, the United States, and Australia, as well as WHO.[31] Between 2011 and 2016, 944 sites were inspected, of which 458 were of common interest, i.e. involved in the manufacturing of products marketed in more than one geographical area. Of these, 49% were located in India, and 36% in China, with the remaining 15% in 16 countries around the world. Sites were inspected 2.9 times on average during the 6-year period, but sites with compliance issues were inspected more frequently than others. During that period, 28% of inspected sites had at least one non-compliant inspection (Regulatory Agencies, 2018[29]). In addition to this, a new pilot phase was launched of inspections of sterile finished product manufacturers located in third countries (European Medicines Agency, 2019[30]). It is important to note, however, that manufacturing site inspections only rarely lead to supply disruptions, and specific procedures exist to minimise the impact on supply[32].

4.3.2. Concentration in manufacturing can increase supply vulnerability

62. The geographic concentration of manufacturing (either at individual sites or in small geographic areas) creates particular vulnerabilities in the event of natural or man-made disasters (e.g. extreme weather events; war or civil unrest etc.). However, publicly available information does not allow a clear evaluation of this risk. While some countries may retain detailed information regarding individual sites of manufacture of regulated products, it is not clear that national regulatory authorities hold this information routinely.

63. In recent decades, API manufacturing for some products has been gradually shifting from Western European countries to India and China, countries with lower labour costs (about one-tenth of labour costs in the United States), transport and infrastructure costs, less stringent environmental regulation, the ability

[30] Austria, Belgium, Croatia, Czech Republic, France, Germany, Hungary, Ireland, Italy, Norway, Romania and Spain.

[31] Canada and Japan joined the programme in 2016 as observers.

[32] For a European example, see the set of documents published by EMA under the section entitled *Guidance for regulators on shortages due to manufacturing or quality issues* available at https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines# guidance-for-regulators-on-shortages-due-to-manufacturing-or-quality-issues-section (last accessed November 2021).

to produce at large scale, and lower barriers to entry (Bumpas and Betsch, 2009[31]). In recent years, China specialised in the first step: transformation of raw materials into intermediates of active pharmaceutical ingredients (APIs), while India specialised in the second step of final API manufacturing stage (ibid.).

64. According to information from August 2019, only 28% of the facilities manufacturing APIs for the US market were located in the United States. The remaining 72% were in the EU (26%), India (18%), China (13%), Canada (2%) and other countries (13%)[33] (Woodcock, 2019[32]). When information is split for sites involved in the manufacture of finished products vs APIs it shows that, for the former, 37% of sites were located in the United States and 24% in India, while for the latter, 31% of sites were located in India and another 31% in EU countries (see Table 4.2 and (U.S. FDA, 2019[18])).

Table 4.2. Distribution of sites involved in the manufacture of medicines for the US market, according to location (% of total sites by category), 2018

	Sites involved in the manufacture of finished products	Sites involved in the manufacture of APIs
Canada	4%	0%
China	8%	14%
EU	18%	31%
India	24%	31%
Latin America	0%	2%
Rest of the Word	10%	11%
United States	37%	12%
Total	***100%***	***100%***

Source: (U.S. FDA, 2019[18])

65. The US FDA further focused its analysis on 370 medicines marketed in the United States and those included in the WHO Essential Medicines List. The data show that 1 079 API facilities worldwide were involved in their production, 21% of which were located in the United States, 15% in China, and the remaining two-third in other countries (Woodcock, 2019[32]). In Canada, national authorities track the source country of all drugs and APIs marketed in the country. Of the close to 10 000 human drugs actively marketed in Canada, approximately 10% are made with an API fabricated in China and approximately 40% are made with an API coming from India[34].

66. Beyond the location of sites in foreign countries, the concentration of manufacturing sites in a single area actually constitute an even greater risk of vulnerability. From a United States perspective, in 2018, about 2 700 sites manufactured one or more products intended for use in the US market: 39% of these sites were located in the United States, 12% in India, 11% in China, 4% in Germany and 4% in South Korea (U.S. FDA, 2019[33]). The number of individual products manufactured at a single site can be high and a small number of sites responsible for production of a large number of products. For example, in China and India, the three sites manufacturing the most products intended for the US market in these countries accounted for 11.2% (of a total of 5 743 products), and 12% (of a total of 15 245 products) of all products intended for the US market and manufactured in these countries (ibid.). Information on the location of manufacturing sites does not appear to have been published for other countries, but a study on insulin supply showed that in 2016, 99% of insulin was supplied by 3 companies relying on 34 potential manufacturers, 15 of which were located in Asia, 10 in Europe and 7 in Latin-America (Beran et al., 2019[34]).

[33] The number of registered facilities making APIs in China more than doubled between 2010 and 2019.

[34] Personal communication, Health Canada, 2021.

4.4. Commercial factors and the policy settings that influence them may also play an important role, particularly for off-patent products

67. **Several studies, including this one, have reported that shortages predominantly affect older, off-patent, medicines**. For example, a study of shortages observed in France showed that older drugs (i.e. those marketed for more than 10 years) were over-represented in shortage data: they accounted for 63.4% of 3 530 pharmaceutical products notified in shortage from 2012 to 2018 while they represented only 45% of medicines on the market (Benhabib et al., 2020[13]). In an analysis of 163 medicines for which shortages were reported in the 5-year period 2013 to 2017, the FDA found that 63% (103) were sterile injectables and 67% (109) were drugs for which one or more generic versions were on the market. Drugs in shortage were older drugs, with a median time since first approval of almost 35 years. The study also revealed that in the year prior to the shortage, these drugs had relatively low prices; the median per unit price[35] was USD 11.05 for the injectables, and USD 2.27 for the oral formulations (U.S. FDA, 2019[18]). Furthermore, a 2019 study in Canada examining shortages notified during 2016-2017 found that the majority of drugs in short supply came from generics companies (Videau, Lebel and Bussières, 2019[12]). These results are consistent with the analysis presented in Section 3. of this report. These findings prompts questions regarding the links between commercial decision making within companies and the evolution of shortages, particularly in the case of off-patent products.

68. In order to understand the nature of drugs subject to shortages, one empirical analysis looked at some of the root causes of shortages in the US market (U.S. FDA, 2019[18]). The analysis compared sales data for individual products before and after the occurrence of the shortage, and compared these with drugs with similar characteristics for which shortages were not reported. The study further compared the "business case" for the two groups of drugs by looking at the share of the MAH's revenue represented by each of the products, as well as the proportion of the revenue contributed by the facility manufacturing the product. The authors reported that for drugs that experienced a decrease in revenue before the shortage, the business case was arguably weak at the *product level*, i.e. demand was falling and it represented, on average, only 0.16% of company revenue compared with 0.34% for drugs with no shortage. For drugs with sales increasing prior to the reported shortage, the business case was arguably weak at the *manufacturing facility level*, i.e. the facility represented a smaller proportion of the company's revenue than for those facilities manufacturing drugs with no shortage. The FDA also found that the market failed to respond in a way that would 'correct' the shortages; only 18% of products had a price increase greater than 50%; and only 42% of products had a significant increase in production by the manufacturer or a new supplier. Finally, only 30% of the products had supplies restored to at least pre-shortage levels within 12 months or by the end of the reported shortage, if less than one year (ibid.).

69. Based on this analysis, the FDA suggested three root causes of shortages (U.S. FDA, 2019[18]):

- **A lack of incentives to produce less profitable drugs**, which reduces firms' motivation to maintain production of old products and also deters market entry of generic manufacturers. The report attributes this to tendering and contracting practices, deemed to contribute to unsustainably low prices.
- **A lack of incentives to upgrade production sites with a view to future compliance with GMP or maintenance of mature quality management systems** that would be expected to improve reliability of supply. This is explained by noting that purchasers do not have the necessary information or incentives/obligations to give a price premium to suppliers with the highest quality and reliability standards.
- **Logistical and regulatory challenges that can impede rapid responses to supply disruptions**. If a company wants to expand its capacity or find a new source of API rapidly, or if a

[35] Per injection for injectable, and per individual tablet or capsule for orally administered medicines

new company wants to enter the market to supply a medicine in shortage, they need to file an application with FDA and await its approval.

70. One aspect that may be specific to the US market are contracting practices. The FDA reported that some contracts include "low-price clauses", that allow group purchasing organizations (GPOs) to unilaterally resile from a contract if a competing manufacturer is willing to supply the same product(s) for a lower price. Indeed, in recent decades, consolidation in the health care sector has provided considerable market power to GPOs which purchase medicines for the vast majority of hospitals. By 2018, the four largest GPOs accounted for about 90 percent of the market for medical supplies in the United States (Bruhn, Fracica and Makary, 2018[35]).

71. Elsewhere, literature exploring the problem in the European context suggests that more insights are needed into the underlying causes of shortages, including the potential commercial drivers. Pauwels et al. (2014[22]) investigated eight medicines shortage reporting systems from seven European countries in 2013 and found that while causes were widely underreported, production problems were suggested to be the principal cause. The authors suggested that the potentially strong link between production problems and market attractiveness should be explored. In early 2014, Bogaert et al. (2015[20]) conducted 21 semi-structured interviews with national authorities, industry, wholesalers and pharmacists from Belgium, France, and the European Union, and from these interviews categorised shortages according to three determinants: manufacturing problems, distribution and supply problems, and problems related to economic aspects, with economic aspects appearing to take a leading role. Furthermore, De Weerdt et al. (2015[21]) explored the influence of legal and regulatory measures in the European pharmaceutical framework (i.e. various EU directives and their manner of implementation in EU member states) on shortages, and found that price and quality regulations were important causes of medicine shortages and unavailability (i.e. when a new medicine is not introduced on the market). According to this paper, external price referencing may have the greatest impact on shortages of patented medicines, while this, in addition to internal price referencing, price capping, and tendering may affect generics. Non-compliance with manufacturing and quality requirements also contributed to shortages in the form of recalls (De Weerdt et al., 2015[21]).

72. Given the complex and global nature of medicine shortages, **more robust data and further research are needed to better evaluate the underlying causes in different settings and contexts**.

5. How countries are addressing medicine shortages

73. Most OECD countries have implemented a number of measures in order to address the issue of medicine shortages (see Box 5.1). However, differing perceptions of the root causes of medicine shortages complicate the effectiveness of measures to prevent them. The following sections describe some of the measures aimed at (1) monitoring the status of shortages (Section 5.1) and (2) mitigating the impact and preventing the occurrence or re-occurrence of shortages (Section 5.2). However, a comprehensive approach combining all three elements and involving dialogue with all relevant stakeholders would be needed to address this problem (Section 5.3).

Box 5.1. A mix of policy measures are used by countries to address shortages

A cross-sectional overview published by Vogler and Fischer in September (2020[1]) presented measures taken or planned as of March/April 2020 in 24 countries, including 16 members of the European Union[1]. Based on an open-ended questionnaire using a pre-defined taxonomy of measures to address shortages, responding countries provided information on national measures (some of which related to COVID-19, although the survey was not planned as a COVID-19 related survey).

Measures used to manage, reduce the impact of, or prevent shortages across the 24 countries included: reporting of shortages to national registers, usually on an obligatory basis by marketing authorisation holders (20/24 countries); simplified procedures for marketing authorisation and distribution of imported substitute products e.g. allowing patient information leaflets in other languages (20/24 countries); regular stakeholder dialogue via formal working groups or taskforces involving marketing authorisation holders, wholesalers, pharmacists, patients, and the public (18/24 countries); financial measures, such as sanctions for failure to supply or non-compliance with inventory or reporting requirements (15/24 countries); established supply reserves for marketing authorisation holders and wholesalers to stock defined medicines in quantities sufficient to last a certain time period (14/24 countries); and provisions imposing export bans or export notification requirements for specified medicines (10/24 countries)

The authors noted that a mix of measures was generally used by countries and with a particular focus on measures managing existing or anticipated shortages rather than addressing root causes. Actions also differed in their intent and scope, with a particular focus on the supply of national markets.

Note: 1, Including Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, Germany, Italy, Latvia, Lithuania, Malta, the Netherlands, Portugal, Romania, Slovenia, Sweden, Albania, Canada, Israel, Moldova, Norway, Russia, Switzerland and the United Kingdom. 2. It is worth noting that by the end of 2019 only five countries surveyed allowed the provision of export bans, and this doubled by mid-April 2020. Source: (Vogler and Fischer, 2020[1]).

5.1. Although many countries monitor shortages systematically, greater harmonisation is needed

74. While most OECD countries have implemented measures such as national registers to monitor shortages, or requiring marketing authorisation holders (MAH) to notify supply disruptions in advance, **reporting requirements differ widely across countries and regions** (see Section 2.3). Three major differences are briefly mentioned below, including the type of products, the timing of advance notice and reported causes for shortage notifications (see Section 2.3 and tables in Supplementary Material 1 for a detailed overview of the differences between countries).

- **First, there is no uniformity in the *classification of products* for which expected shortages must be notified**. While MAHs must report any expected or current shortage in some countries (e.g. Belgium, Canada, Norway), in other countries they are only required to do so for products included in pre-defined lists of "essential medicines" (e.g. France, Switzerland, United States). Furthermore, the number of medicines listed for which shortages would be considered "critical" varies across countries. In proposals to work towards a common definition of shortages, the World Health Organization has suggested focusing on medicines "identified as essential to the health system" (Hedman, 2016[36]). Some registries also report discontinued products as shortages, and this may inflate their numbers relative to those countries that do not.
- **A second difference is in the *timing of advance notice***. While some countries require MAHs to notify expected shortages six months in advance if possible, in others the time limit is much shorter, and some do not impose any timing requirement. This affects the capacity of regulatory authorities and other stakeholders to anticipate risks and adopt mitigation strategies.
- **A third difference pertains to the *reporting of the reasons* for shortages**. While MAHs are generally required or encouraged to explain the reasons behind expected shortages, **there is no standardisation of causes, which not only makes the analysis of causes complex but also compromises cross-country comparisons** (see Section 4.).

75. In recent years, steps have been made to harmonise shortage reporting at the EU level, with the European Medicines Agency (EMA) and Heads of Medicine Agencies (HMAs) in July 2019 issuing a *guidance for the detection and notification of shortages of medicinal products for MAHs in the EEA* as a step toward harmonised reporting (EMA, 2019[8]). The document provides a definition of "a shortage", as well as guidance on when and to whom MAHs are expected to notify expected shortages, and a template to report a notification to relevant national agencies and/or the EMA. MAHs are not obligated to comply with this guidance but **this constitutes a real opportunity to harmonise reporting and cooperation in the area, to tackle shortages.** As previously mentioned, this guidance will be tested and implemented through a dedicated pilot phase.[36]

76. In addition, countries would indeed benefit from a harmonisation of a number of aspects of medicine shortages notifications including, but not limited to:

- Definitions of a shortage and subsequent notification;
- Indicators for expected shortages;
- Types of shortages to be notified (e.g. actual versus expected, current versus resolved, temporary versus permanent);
- Duration of the shortage;
- Extension of reporting systems to include other downstream stakeholders (wholesalers, pharmacists and doctors) to facilitate early reporting of unavailability of medicines (early warning systems) (see Box 5.2).

[36] Delayed due to COVID-19 pandemic.

- Where shortages are published; and
- Who is required to report shortages

77. Data collected should ideally be made publicly available with a harmonised template (e.g. active substance, anatomical therapeutic chemical [ATC] classification, brand name/strength/pharmaceutical form/pack size, actual [or anticipated] start date, actual [or expected] end date, cause), and information communicated to health care professionals, patients, and the general public.

78. Greater harmonisation of shortage reporting, including early warning procedures, at least at the regional level, would:

- Ensure robust within and cross-country comparisons;
- Enable better understanding of the impact on patients
- Improve understanding of the root causes; and
- Encourage the development and evaluation of policy measures to mitigate and prevent them.

Box 5.2. Example of a cross-border early warning system at pharmacy level: CISMED

CISMED (Centre for Information Supply of Medicines) is a pharmacy-based information system developed in Spain that detects medicine supply issues automatically and in real time at the level of the patient. The information collected from pharmacies can be used by authorities to predict medicine shortages at regional and national level. Under a project funded by the European Commission as part of the Digital Health Europe twinning scheme and beginning in November 2019, Spain has worked together with Portugal, France and Italy to set up a mechanism, based on CISMED, for cross-border exchange of information on medicine supply issues. The project showed that it is feasible to set up a mechanism to share information on medicine shortages among countries. The next step is to explore the implementation of such a pharmacy-based reporting system at European level.

Source: See https://digitalhealtheurope.eu/news/pharmacy-based-system-for-medicine-shortage-detection-system-cismed-sets-up-mechanism-to-exchange-information-on-medicine-shortages-among-four-countries/ (accessed October 2021).

5.2. Actions to mitigate and prevent shortages are taken at different points in the supply chain

79. There are many examples of measures taken along the supply chain to mitigate or prevent shortages, the impacts of which are yet to be assessed. These actions may target the logistics and distribution issues (Section 5.2.1), manufacturing and quality issues (Section 5.2.2), and the economic / commercial drivers (Section 5.2.3). These efforts should be accompanied by improved efforts in communication and transparency about shortages to health professionals, patients, and the general public (Section 5.2.4). Table 5.1 provides a brief overview of some of these measures with country examples, while Box 5.3 explores the unique case of the COVID-19 pandemic.

Table 5.1 Examples of mitigation strategies used by national authorities to address shortages

Strategies	Country Examples
Regulatory measures (e.g. special permits for import, language exemptions, multi-language labelling, case-by-case authorisations for use)	Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Italy, Latvia, Lithuania, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, United Kingdom
Financial sanctions (e.g. for non-supply, non-compliance to reporting requirements, non-compliance to stocking requirements)	Canada, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Netherlands, Portugal, Slovenia, Sweden, United Kingdom
Measures relating to exports (e.g. export or parallel export bans, export notification lists)	Austria, Belgium, Czech Republic, Estonia, Finland, France, Greece, Hungary, Israel, Italy, Latvia, Norway, Portugal, Slovak Republic, Spain, United Kingdom
Medicines supply reserves (by MAH and wholesaler; others may have established national, pharmacy or hospital stocks; supply reserves may be for select products)	Canada, Denmark, Germany, Finland, Israel, Latvia, Lithuania, Norway, Portugal, Switzerland, United Kingdom
Risk management plan required by national authorities	France, Hungary
Multi-stakeholder collaborative action (e.g. working group, steering committee, taskforce, meetings, bilateral discussions, case-by-case analysis)	Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Israel, Ireland, Italy, Latvia, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom
Recommendations by national authorities for use of alternative treatments	Belgium, France, Greece, Hungary, Lithuania, Netherlands, Sweden
Measures relating to communication / information sharing to health care professionals	Belgium, Norway, Hungary, Portugal

Source: Adapted from (Vogler and Fischer, 2020[1]) and the HMA/EMA Task Force on the Availability of Authorized Medicines for Human and Veterinary Use's summary of the individual situation in EU Member states available at https://www.hma.eu/598.html, updated on 10 March 2020 and again in August 2020. Additional information provided by national authorities in early 2020.

Box 5.3. Impact of COVID-19

With the onset of the COVID-19 pandemic, demand for critical medicines surged worldwide, particularly in the early days of the crisis. Reduced manufacturing capacity, export bans and other trade restrictions, logistical problems and transport barriers, panic-buying, and national stockpiling all exacerbated the risks of shortages. In this unprecedented situation, neither the drivers of shortages, nor the approaches to their mitigation, are necessarily representative of those of pre-pandemic times.

Several governments enacted temporary restrictive trade measures of vital medical supplies, including prescription medicines (OECD, 2020[25]; OECD, 2020[26]), further exacerbating existing shortages, especially in non-producing countries. The measures included export bans and additional licencing requirements (i.e. new requirements for obtaining export licenses that may specify which exporters may sell products abroad, in what quantities) thereby increasing both complexity and costs of exports.

At the European Union level, various coordinated responses were taken. On 15 March 2020, an EU-wide regulation introduced export authorisations on personal protective equipment (PPE) outside the EU (requiring assessment of the needs of Member States prior to authorisation). As a result, most Member States lifted their export restrictions on these products. This measure expired towards the end of May and was not extended or replaced. On 3 April 2020, the European Commission enacted a measure to approve requests from EU countries and Britain to waive customs duties and VAT on the import of medical equipment, including PPE, from non-EU countries (effective from 30 January 2020 to 31 July 2020). On 8 April 2020, the European Commission issued *Guidelines on the optimal and rational supply of medicines to avoid shortages during the pandemic* and urged Member States to lift export bans and restrictions on medicines (including intermediates and active pharmaceutical ingredients) and to avoid national stockpiling, including at the local level of wholesalers, pharmacies and hospital pharmacies.

The European Medicines Agency (EMA), working together with EU Member States and the pharmaceutical industry, launched an enhanced fast-track monitoring system to help prevent and mitigate supply issues involving crucial medicines used for treating COVID-19 patients. The monitoring system involves each pharmaceutical company appointing an industry single point of contact (i-SPOC) to gather information on medicines used for the treatment of COVID-19 which could be at risk of supply disruptions. The EMA channels aggregated information on supply shortages to the EU Executive Steering Group on shortages of medicines caused by major events, which decides on those EU-level coordinated actions necessary to optimally address these supply shortages (irrespective of their licensing route). The EMA also published guidance on regulatory expectations and flexibility during COVID-19; under Article 63(3) of Directive 2001/83/EC, Member States may "*grant full or partial exemption to certain labelling and packaging requirements"* for crucial medicines for use in COVID-19 patients. This includes accepting that product information may not be translated into the official language in the event of severe availability problems, and that national specific information may not appear or the presentation may differ from that authorised in the Member State.

Sources: See https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf; https://www.ema.europa.eu/en/news/guidance-regulatory-requirements-context-covid-19-pandemic; https://www.ema.europa.eu/en/news/launch-enhanced-monitoring-system-availability-medicines-used-treating-covid-19; last accessed November 2021.

5.2.1. Actions targeting logistics and distribution issues are among the more established practices

Simplified regulatory procedures

80. In the event that an unavailable medicine has no suitable alternative, countries may **use simplified regulatory procedures for importation, marketing authorisation and dispensing of medicines**. For example, importation of products without marketing authorisation is allowed in each of 20 EEA countries surveyed by Bochenek et al. (2018[9]), although special permission from the national regulatory agency may be required. In anticipation of such events, small countries, such as the Baltic States and Nordic countries, have implemented multi-language labelling of packages to facilitate imports from abroad. Some countries also allow for language exemptions for product labelling, such as for the patient information leaflet.

Imposing requirements on suppliers

81. In Europe, **several countries have introduced Public Service Obligations (PSOs)** for MAHs or wholesalers, but these are not always fully enforced. Within the EU, Directive 2001/83 Article 81 states that "the holder of a marketing authorisation for a medicinal product and the distributors of said medicinal product…shall, within the limits of their responsibilities, ensure appropriate and continued supplies of [the] medicinal product to pharmacies and persons authorized to supply medicinal products so that the needs of patients in the Member State in question are covered"[37]. Most EU countries have adopted this directive in their national legislation to impose PSOs to MAHs. Of 20 EEA countries included in the study, all have PSOs, applying either to the entire market or to publicly funded medicines. In Poland, for example, MAHs must guarantee a certain volume of sales and may be fined if they cannot deliver. In Germany, the PSOs of wholesalers are linked with the right to be supplied by the MAH (Bochenek et al., 2018[9]).

82. According to the European Healthcare Distribution Association – GIRP - Article 81 paragraph 2 of the Directive 2001/83/EC as amended, should be interpreted and set-out in national legislation in a manner that places independent or separate obligations on both MAHs and pharmaceutical full-line wholesalers. Consequently, according to GIRP, this is why national legislation should also provide for and duly enforce an auditable right to be supplied for pharmaceutical full-line wholesalers to be appropriately and continuously supplied by MAHs with the full range of products in order to fulfil the needs of patients in the Member States in an appropriate manner.

83. Outside the EU, supply requirements are also imposed. In Switzerland, PSOs to MAH are imposed with an obligation of stockpiling in quantities agreed with the Federal Office for National Economic (FONES) (Bochenek et al., 2018[9]). In Australia, the Community Service Obligation (CSO) system aims to ensure all Australians have access to any publicly-funded medicine, at any community pharmacy, usually within 24 hours[38]. Under the CSO Funding Pool arrangements, direct payments are provided to eligible CSO wholesalers who meet the above conditions, together with meeting certain CSO compliance requirements and service standards.

84. Several countries impose **financial sanctions** related to medicine shortages, but it is not known whether they are fully enforced. One study (Vogler and Fischer, 2020[1]) reported that financial sanctions were in place for non-compliance in -supply in six countries, non-compliance with reporting requirements in six countries, and non-compliance with stocking requirements in four countries.

[37] See https://ec.europa.eu/health/system/files/2016-11/dir_2001_83_cons_2012_en_0.pdf (accessed June 2020).

[38] See https://www1.health.gov.au/internet/main/publishing.nsf/Content/community-service-obligation-funding-pool (accessed November 2021).

Provisions to impose export restrictions

85. In an effort to protect national supply, some countries have **provisions for export (or parallel export) bans or requirements for export notification for specified medicines.** For example, EU legislation also allows for the **limiting of exports if public health is endangered in an EU Member State**. Of 20 EEA countries included in the review by Bochenek et al., 14 have introduced legislation allowing the limiting of exports and 8 have deployed it (Czech Republic, Estonia, France, Greece, Poland, Portugal, Slovak Republic and Spain). Greece, for example, can ban exports for medicines which are ''unique or irreplaceable''. In 2015, Poland established a list of products particularly susceptible to shortages for which wholesalers must obtain permission to export. However, as illegal exports persisted, an integrated system was introduced in 2018, which allows tracking of every product in the country (Bochenek et al., 2018[9]). France can ban exports for products of major therapeutic interest (MITM)[39] in case of risk of shortage, and wholesalers are not allowed to export MITM drugs that are in a current or predicted shortage. All operators are at risk of administrative or financial penalties in case of non-compliance (Benhabib et al., 2020[13]). The COVID-19 pandemic revealed that many countries used trade restrictions to monitor and/or ban exports of pharmaceuticals and other products (Section 4.2.2). However, such actions can actually increase international scarcity and risk of shortage.

Supply reserves

86. **Supply reserves of essential medicines and medical equipment by MAH or wholesalers**, e.g. at national and at supra-national (e.g. European) level have also been cited as strategies to mitigate the impact of medicine shortages (Vogler and Fischer, 2020[1]). For example, the Canadian Public Health Agency maintains the National Emergency Strategic Stockpile for use in emergencies such as pandemics. In Finland, MAH are obligated to stock some critical inpatient medicines; MAH, importers, institutions (e.g. hospitals) and the National Institute for Health and Welfare are obligated to stock a list of more than ~1500 medicines for between 3 to 10 months (ibid.). During the COVID-19 pandemic, the Danish Critical Supply Agency has managed national stocks of personal protective equipment and other critical resources, as well as the EU medical rescEU-stockpile[40].

5.2.2. Addressing vulnerabilities stemming from manufacturing and quality issues

87. A number of measures have been taken by countries targeting manufacturing and quality issues. For example, **several countries require MAHs to adopt risk management plans to prevent shortages.** In France, for example, since 2016, MAHs and other operators have been required to develop shortage management plans, and they risk administrative or financial penalties in case of non-compliance (Benhabib et al., 2020[13]). In Hungary, the law requires risk management plans and specifies possible risk minimisation tools. The 2018 FDA report recommends the adoption of legislation to enable the FDA to require MAHs of certain drugs to develop risk management plans with periodic risk assessments to identify vulnerabilities in their manufacturing supply chains and develop plans to mitigate the risks of the identified vulnerabilities (U.S. FDA, 2019[18]). Countries may also ensure that contractual requirements are in place for maintaining appropriate inventory or safety stock, multisite sourcing with higher manufacturing capacity reserves, and mandating levels of redundancy where there are multiple inputs into the supply chain. The

[39] As mentioned earlier in the report, *Médicaments d'Intérêt Thérapeutique Majeur* [MITM]) are drugs for which a shortage would be life-threatening or represent a loss of treatment opportunity for patients with a severe disease.

[40] See https://sfos.dk/english/ (accessed November 2021).

EMA has also published a set of documents intended to support EU regulators in the assessment of shortages due to manufacturing and quality issues, including GMP compliance problems[41].

5.2.3. Preventive measures, particularly in the case of off-patent products, may need to target economic or commercial drivers

88. Measures targeting the commercial drivers of shortages and the policy settings that influence them may require appropriate incentives to shape markets and bring new suppliers.

89. For example, in the United States, a report by the FDA recommended to focus on economic incentives to prevent shortages. More precisely, the FDA report recommended to (U.S. FDA, 2019[18]):

- **Better understand contracting and tendering practices** that may contribute to shortages and promote model contracts that do not lead to unsustainably low prices.
- **Create a rating system that incentivises drug manufacturers to invest in achieving quality management system maturity**. The idea is to develop a system to measure and rate the quality management maturity of individual manufacturing facilities, based on objective indicators. With such a system, companies could - beyond compliance with Current Good Manufacturing Practices (CGMPs) - adopt management systems to detect vulnerabilities and address them in order to prevent the occurrence of problems (e.g. securing sourcing from at least two API producers). With information on the performance of quality management systems - through a rating system - payers, purchasers, and Group Purchasing Organisations could provide them with a competitive advantage (higher prices, higher market shares) in contracts.
- **Promote sustainable private sector contracts**. The combination of the two latter measures could help to provide manufacturers with sustainable risk-adjusted returns on their investment in launching or continuing to market prescription drugs, especially older generic drugs; and to reward them for mature quality management

90. Relying on market mechanisms and incentives, Denmark, Norway and Iceland decided to pilot joint public procurement with the aim to foster supply of older medicines and prevent recurrent episodes of shortages due to their small market size. (Rommelhoff et al., 2019[37]).

91. As seen in sections 3. and 4. , shortages appear to affect predominantly older, no longer patent-protected medicines, for which generic supply has been possible for some years. The increased availability of generics and growing pressures to control health spending have driven the prices of these medicines down, sometimes substantially. This dynamic has been useful to expand access and contain costs, but may at times lead to prices that are not necessarily sustainable nor commercially attractive for producers. Indeed**,** if prices fall below the marginal cost of production, or revenues deemed insufficient, manufacturers may withdraw these products from the market. The European Society of Medical Oncology recently conducted a study of the relationship between pricing and shortages of cancer medicines (Vyas et al., 2019[38]). It found that older, off-patent, relatively inexpensive medicines are more frequently declared in short supply. This situation is even more problematic when it is understood that these products often constitute the backbone of a number of important chemotherapy protocols. **Further analysis is needed to examine policy settings that ensure markets appropriately incentivise the continued production of off-patent products needed by patients.**

92. Overall, **diversification of supply is key to security of supply**. This includes keeping existing players in the market as well as the introduction of new ones. In the case of generic products, new players

[41] See section entitled *Guidance for regulatory on shortages due to manufacturing or quality issues,* available at https://www.ema.europa.eu/en/human-regulatory/post-authorisation/availability-medicines#medicine-shortages-section (accessed November 2021).

are unlikely to enter the market as the regulatory hurdles and required investment are too high. As such, it is a priority to keep these suppliers to ensure adequate supply of these products.

5.2.4. Prevention and mitigation measures should be accompanied by renewed communication and transparency efforts

93. **Seeking collaborative actions with stakeholders is pivotal to mitigating the impact of expected or notified shortages**. As found by Vogler and Fischer (2020[1]), many countries implement such measures, with at least 18 countries surveyed reporting regular meetings with relevant stakeholders, often in the form of formal working groups or a specially established task force involving MAH, wholesalers, pharmacies, hospitals, patients and the public. Other coordinated corrective actions involving the competent authority and various stakeholders (e.g. MAHs, suppliers of alternative products, wholesalers, pharmacies, hospitals etc.) are also taken on an as-needed basis.

94. While many countries post shortage information on their respective websites, **further efforts are needed to improve communication and transparency of shortages to health professionals, patients and the general public**. In Norway and Belgium for example, the electronic alerts on medicine shortages are fed directly into the electronic prescribing system to alert prescribers at the time or prescribing. Another example is the *Dossier Pharmaceutique Ruptures* system in France, which is deployed in 15 376 pharmacies (May 2020, +/- 70% of all pharmacies) and developed/managed by the French Chamber of Pharmacists. This tool is integrated in the pharmacy dispensing software and is used to communicate on expected or observed medicine shortages. Community pharmacists can also notify unavailability automatically via this system, with a notification sent when a product cannot be obtained within 72 hours[42]. In addition, the EMA and HMA published in 2019 a guidance with recommendations for EU national competent authorities as well as EMA on better communicating shortages to the public[43].

95. Competent authorities in some countries make **recommendations on alternative treatments in case of shortages or help to identify other solutions**. For instance, in Spain, the national regulatory agency provides information on possible alternatives on their website, as do agencies from Belgium, the Czech Republic, France, Greece, Hungary, Italy, Norway and Sweden. In the case of a verified shortage in the Netherlands, the system actually provides the pharmacists with four steps: substitution, pharmaceutical alternative, import, or pharmacy preparation. In Japan, The Ministry of Health, Labour and Welfare (MHLW) instructs pharmaceutical companies, upon reporting of current or expected medicine shortages, to seek cooperation from other pharmaceutical companies that produce alternative products or to consult with relevant medical society for possible solutions. In Ireland, when a MAH notifies the Health Products Regulatory Agency (HPRA) of a pending shortage, the HPRA contacts the relevant Health Service Executive Delivery unit. The Acute Hospitals Drug Management Programme works with relevant National Clinical Programmes to identify clinically appropriate alternatives as well as clinical guidance approved by the National Clinical Programme lead if there has been notification of a shortage which could be expected to have a high impact in the acute hospital setting. In the United States, by contrast, information on alternative medicines is not provided as the Food and Drug Administration has no competence in the “practice of medicine”, but the agency provides a link to an alternative database

[42] See more information available at http://www.ordre.pharmacien.fr/Le-Dossier-Pharmaceutique/Ruptures-d-approvisionnement-et-DP-Ruptures (accessed June 2020).

[43] See *Good practice guidance for communication to the public on medicines’ availability issues* available at https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guidance-communication-public-medicines-availability-issues_en.pdf (last accessed November 2021).

maintained by the American Society of Health System Pharmacists (ASHP), which contains information on drugs in shortage and suggests alternative medicines[44].

96. Overall, there is a **paucity of impact assessments of national policies to address medicine shortages and countries would benefit from undertaking such assessments to identify good practices**. For example, Di Giorgio et al (2019[39]) reported on a collaboration project in Italy whereby an ad hoc technical forum of stakeholders was created aimed at building consensus around interpretation and enforcement of the existing regulatory framework for the management of the distribution of medicines. Stakeholders included central and local administration, associations of MAHs, distributors, pharmacists, and health professionals. The success of this collaboration was evaluated through some indicators of unavailability due to distribution-related issues for key medicines and considered to have reduced the extent of the problem (Di Giorgio et al., 2019[39]).

5.3. Countries would benefit from national strategic action plans and cross-country collaboration

97. As seen, shortages have multiple and intertwined causes and no single policy measure will be enough to combat this issue. Crosscutting actions to mitigate and prevent shortages involve assessing the potential impact of the shortage (see Box 5.4), engaging with stakeholders, and communicating downstream to others including health professionals and the public as appropriate. It is important for countries to implement a comprehensive strategy, for example, in the form of **a national strategic action plan (or risk management plan) that covers *monitoring, mitigation, and prevention of shortages*** (see Box 5.5 as an example from France).

98. However, even comprehensive national action plans would benefit from enhanced international cooperation and engagement with all stakeholders. The EMA/HMA initiative is a first step in the right direction but further initiatives are needed across regions and greater competence needs to be given to regional and international organisations to be able to implement more ambitious action plans. These channels of communication are already established among stringent regulatory authorities on issues such as mutual recognition and other forms of regulatory cooperation (Luigetti et al., 2016[40]). **These could be used to facilitate the development of coordinated policy measures that would magnify their effect on this issue.**

[44] See FDA Drug Shortages Frequently Asked Questions available at https://www.accessdata.fda.gov/scripts/drugshortages/dsp_faq.cfm#noalternativesprovided (accessed June 2020).

Box 5.4. Assessing the potential impact of a shortage at the outset can guide mitigation strategies

Impact assessment tools can be used to predict the impact of an anticipated or actual shortage, and assist in development of mitigation actions. For example, Musazzi et al (2020[23]) proposed a harmonised tool for evaluating the impact of medicine shortages in European countries. This tool provides an overall score for the shortage impact of a medicine as high, medium or low, based on three levels 1) disease to be treated, 2) availability of alternatives, and 3) market share in a specific country. Products are given a score for each level based on three or four alternatives, which are then aggregated into the overall impact score. Based on these scores, the authors present hypothetical decision-trees to assist national decision-making for risk management strategies (ibid.).

Similarly, the Irish Health Products Regulatory Authority uses a framework to address medicine shortages, which includes impact assessment based on 1) availability of therapeutic alternatives, and 2) the expected impact on patients[1]. The former grades therapeutic alternatives into five categories, "exact", "similar", "appropriate", "possible", or "none", while also considering approved indications of alternatives as well as likelihood of availability, feasibility of substitution, and patient safety. The impact on patients is determined by taking into account the consequence of the shortage on the progression of the disease, and categorised as "mild", "moderate", or "high". The overall impact level of the shortage is then assessed according to a defined matrix based on the above considerations.

Source: Authors as cited. 1. See http://www.hpra.ie/docs/default-source/Shortages-Docs/medicines-shortages-framework.pdf?sfvrsn=2, (accessed October 2021).

Box 5.5. France's government program to address medicine shortages

In 2019, France published a four-year strategic action plan to address medicine shortages. This plan entails 28 measures gathered in 4 different strategic pillars.

- The first pillar aims at promoting greater transparency and communication between stakeholders of the pharmaceutical sector to better anticipate, prevent and address shortages. Measures include, among others, the development of solutions for electronic notification of shortages for all the actors of the distribution chain.
- The second pillar intends to reduce the number and impact of shortages via, for instance, an enhanced substitution right for pharmacists and revised procurement practices for hospitals.
- The third stream of work aims at increasing international collaboration in the field of medicine shortages. Support to a relocation of production facilities to Europe and joint procurement are part of the measures mentioned.
- Finally, the last pillar of the plan will focus on revising the overall governance of this health issue, which includes the establishment of an inter-ministerial taskforce to follow-up the implementation of the various measures detailed in the national action plan.

Source: (French Ministry of Health, 2019[41])

6. Conclusions

99. Shortages of medicines are a complex global problem that has been receiving increasing attention in recent years. The onset of COVID-19 and associated supply disruptions have further increased the importance of this issue in the global health policy agenda. The aim of this paper was not to attempt to address all aspects of such a complex issue, but to develop further insights into the extent and nature of the problem, and explore some of the root causes and approaches to mitigation. While the paper focuses on the situation in OECD countries, its main findings will arguably be relevant to all countries and stakeholders given the increasing globalisation and interdependence seen in medicine supply chains in the past 25 years.

100. Despite substantial differences in both the definitions of shortages and in national monitoring mechanisms, it is clear that in most OECD countries notifications of anticipated and actual medicine shortages by marketing authorisation holders (MAH) have increased substantially in recent years. Between 2017 and 2019, the numbers grew by more than 60% in the 14 countries for which this analysis was undertaken. The shortages did not affect all types of products evenly, however; more than half of all shortage notifications were concentrated in three pharmaco-therapeutic areas: medicines targeting the nervous system, cardiovascular medicines, and anti-infectives. For 62% of active substances with at least one notification over the time period, shortages were notified in more than one of these 14 countries. While this analysis did not consider a temporal component *per se*, this suggests that many shortages are not country specific. It was, however, difficult to quantify the extent to which shortage notifications in this analysis gave rise to adverse effects on patient health, since a given shortage notification does not necessarily imply a shortage that impacts patients if appropriate alternatives remain available.

101. The multifactorial nature of medicine shortages confounds root cause analysis, with different stakeholder perceptions and poor data quality further complicating the issue. There are many factors that may contribute to medicine shortages, from large demand shocks (such as in the case of COVID-19), to more underlying structural issues such as market incentives (e.g. unsustainably low prices in some off-patent markets). The complexity, and to a certain extent opacity, of this industry makes it very challenging to identify the true drivers of shortages and their respective weights.

102. On the supply-side, logistics and distribution issues are exogenous factors that can understandably result in delivery delays or disruptions thereby contributing to shortages. With pharmaceutical supply chains being often highly complex, involving multiple steps and stakeholders, and frequently distributed across multiple countries and/or locations, any step in the production process can be a source of vulnerability for supply. However, while internationalisation of medicine supply chains is often singled out in policy debates as a factor increasing risks to the supply of medicines, the evidence is not compelling. Moreover, internationally disruptive events such as COVID-19 have shown that trade barriers can contribute to supply disruptions, and that trade is an essential tool to maintain availability at the global level. As no one country is able to produce all the necessary components and medicines for its population, internationalisation could be seen as a means of reducing risks through diversification of channels of supply.

103. From the available information, the majority of shortages reported by MAHs were the result of manufacturing and quality issues. Quality issues may arise at the level of the manufacturing facility (leading to suspension or closure of an entire facility), or at the level of a specific production process in a given

facility (leading to an issue with one or more batches of a product). Linked to this, policy debates also point to the issue of the concentration of manufacturing, or limited availability of manufacturing facilities to produce certain categories or components of medicines, as an additional source of supply vulnerability. However, the effect is difficult to evaluate based on available information. In general, ensuring that the manufacturing of particular components is not highly concentrated at one or few manufacturing sites or in small geographic areas, could reduce the overall vulnerability of medicines' supply to various types of risks (such as quality issues, natural disasters, conflict or trade restrictions), but may not address what appears to be another important underlying driver of shortages, i.e. lack of commercial incentives.

104. It appears that commercial factors, and the policy settings that influence them, may play important underlying roles in propagating medicine shortages, though further analysis is warranted. Several studies, including this one, have reported that shortages predominantly affect older, off-patent, medicines. Regulation and reimbursement policies, such as those that favour unsustainably low prices, may influence commercial decisions, and subsequently put supply at risk. In the United States, for example, an empirical analysis identified three root causes, key among them a lack of incentives to produce less profitable drugs, which may be attributed to tendering and contracting practices. The analysis also cited lack of incentives to upgrade production sites or maintain quality management systems as another root cause. There are also suggestions that similar issues are implicated in Europe, but the links between production problems and market attractiveness warrant further exploration.

105. To improve shortage monitoring, mitigate the impact of shortages or prevent future occurrence or re-occurrence of shortages, OECD countries have already implemented a number of individual measures. Most OECD countries have national monitoring systems, but greater harmonisation of these systems would allow more robust within- and cross-country comparisons, and to better understand the impact on patients, the underlying root causes and effects of policy measures. This, in turn, would be useful to frame policies to better mitigate and prevent future shortages. Countries have implemented a number of measures in an effort to mitigate logistics and distributions issues, such as simplified regulatory procedures, imposing requirements on suppliers, and security of supply measures. However, evidence from the US, which may or may not be generalisable, suggests that preventative measures should target economic and commercial drivers, particularly in the case of off-patent markets. To date, however, there is a paucity of impact assessments of national policies to address medicine shortages and further research is needed to identify best practices.

106. Overall, the complexity of medicine shortages renders simple explanations insufficient to delineate the issues, and single policy measures inadequate to address them. As such, it is important for countries to implement multifaceted strategies addressing monitoring, mitigation, and prevention, and to involve stakeholders in developing and implementing these, and to also recognise the importance of downstream communication to health professionals and patients. It is evident that more robust data and further analysis of the origin and extent of medicine shortages, and of effective measures for prevention and mitigation, are needed. However, it is nevertheless also clear that the way forward should involve a global approach that engages all relevant stakeholders, and addresses policy settings that lie outside the healthcare sector.

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Annex A. Taxonomy of medicine shortages

Table A A.1. A proposed taxonomy of medicine shortages, including some examples

Demand-side factors			*Supply-side factors*			*External factors affecting demand and/or supply*
Exogenous factors that may lead to an increase in demand			*Exogenous factors that may lead to a reduction in supply*		*Endogenous factors that may lead to a reduction in supply*	
Patient-level	*Provider-level*	*System-level*	*Logistics and distribution problems (and supply chain management)*	*Manufacturing and quality problems*	*Economic / commercial factors / policy decisions*	
Stockpiling Shortage of product with similar indication(s) Changes in health care needs	Changes in prescribing practices	Stockpiling Changes in prescribing guidelines or diagnostic criteria Changes in coverage Changes in pricing, GDP growth, procurement	Transport disruptions Other distribution issues Trade barriers Supply quotas and rationing Inventory and storage practices	Quality issues Inventory and storage practices Temporary (or permanent) suspension of production, manufacturing site closure or relocation Limited manufacturing capacity Shortage of inputs	Portfolio management Failure to meet GMP standards Decisions to limit or consolidate manufacturing	Public health crises Natural or human induced disaster Conflict Industrial action Regulatory requirements Pricing and reimbursement policies Public policy

Source: Authors based on review of the available literature, including (Acosta et al., 2019[4]; Benhabib et al., 2020[13]; U.S. FDA, 2019[18]; Bogaert et al., 2015[20]; De Weerdt et al., 2015[21]; Pauwels et al., 2014[22]; Musazzi, Di Giorgio and Minghetti, 2020[23]) and http://girp.eu/sites/default/files/documents/addressing_the_root_causes_of_medicines_shortages_-_eu_supply_chain_stakeholders_views_on_root_causes_and_solutions.pdf , published 6 December 2019 (accessed June 2020).